Biotherapies and Bioproductions

Preface

Sylvie Retailleau, Minister for Higher Education and Research

Introduction

Jean-Marc Grognet, Advisor to the Scientific Director of Fundamental Research at the CEA and **Bernard Celli** Vice-Chairman of the Economic Committee for Health Products

Making France a leader in biotherapies and biomanufacturing

Michel Rao, Deputy Director of the Health, Consumer Goods and Agri-food Industries Directorate General for Enterprise and **Élodie Pliquet,** Biotechnologies, Biotherapies and Bioproduction Project Manager, Directorate General for Enterprise

The development of new biotherapies is crucial to personalised precision medicine, but it also represents a major economic challenge. France has recognised the importance of this sector and has already invested in programmes to support innovation and the production of biomedical products.
The government has launched an acceleration strategy for 2022 with a budget of €800 million to make France the European leader in biomanufacturing. The main thrusts of this strategy include ensuring a continuous flow of innovations from academic research, simplifying market access for innovative therapies, developing industrial facilities and strengthening the structure of the industry.
If this strategy is to succeed, the number of jobs in the sector needs to double, new biotech companies need to emerge and at least 15 new biomedicines need to be produced by 2030.

A national challenge

The Grand défi biomédicaments

Emmanuel Dequier, Head of Industry Relations at the Directorate General for Research and Innovation, Ministry of Higher Education and Research

With the arrival of biomedicines, the drugs industry is undergoing a veritable revolution. These drugs, which make it possible to treat hitherto incurable cancers or genetic diseases, are bringing about a profound transformation of the healthcare industry, with the deployment of new production technologies and a host of challenges still to be met in the industrialisation of the most innovative treatments. The Grand défi biomédicaments and then the *Biothérapie et Bioproduction de thérapies innovantes* acceleration strategy have laid the foundations for structuring the sector so that France can become a European leader in the production of biotherapies.

The role of the Health Innovation Agency (AIS)

Lise Alter, Chief Executive Officer of the Agence de l'Innovation en Santé (AIS)

In the wake of an immensely transformative pandemic, the government has responded with a strategy designed to make France the leading European nation in terms of innovation and sovereignty in healthcare. This strategy takes the form of the Health Innovation Plan 2030, the health component of France 2030, with a budget of €7.5 billion and a dual ambition: to transform the key health sector over the long term, while positioning France as the innovation leader of the future. The Health Innovation Agency (Agence de l'Innovation en Santé - AIS) is the cornerstone of this strategy, and its mission is to anticipate, accelerate and simplify access to innovations in France across the entire value chain. A genuine revolution for patients, the healthcare system and industry, innovations in the field of biotherapies and bioproductions are expressly supported by the AIS in order to facilitate their integration into the ecosystem and make them accessible to as many people as possible as quickly as possible.

France Biolead, the biomanufacturing sector for biomedicines

Laurent Lafferrère, Managing Director of France BioLead

France BioLead, the French biomanufacturing sector, brings together all the players in this field: manufacturers (pharmaceutical and biotech companies, CDMOs, CROs, equipment suppliers, suppliers of technological solutions and consumables), academic research, training organizations, competitive clusters, professional associations and unions.

Its missions are to structure, lead, accompany and promote a unique French biomanufacturing industry, with the support of the French government, to make France a leader in Europe and restore its independence and sovereignty in this sector.

The industry's major objectives for 2030 are to double the proportion of biomedical products produced in France, as well as the number of jobs in the sector (from 10,000 to 20,000), and to enable the emergence of at least 1 new biotech start-up and 5 new biotech mid-size companies.

Biotherapies: adapting to the specific characteristics of advanced therapy medicinal products

Thierry Hulot, Chairman of Leem and Chairman and CEO of Merck in France

The widespread use of biomedicines, in particular advanced therapy medicinal products, brings with it a host of new issues. To best support their arrival on the French market, the pharmaceutical industry has identified three main challenges for the healthcare system, relating to clinical research, intra-hospital organization and the patient pathway, all of which will undergo major changes.

Biotechnology, the industry of today and tomorrow

Chloé Evans, Assistant to the Managing Director, in charge of sector studies and international relations, France Biotech, **Clara Magi**, Chief of Staff at France Biotech and **Franck Mouthon**, Chairman of France Biotech

Thanks to their very innovative, often personalised approach, biotechnologies in healthcare, due to their precision and high potential medical impacts, as well as their costs, development time, and risks, represent a paradigm shift in terms of patient care. Mainly the product of French academic and public-sector research – a key factor in the sector's excellence – French biotech companies developing biopharmaceuticals still face production challenges on the territory, despite efforts made in recent years. Investment must also be encouraged, to ensure the country's attractiveness and sovereignty. Investments in healthcare are widely supported by French public authorities.

A challenge for fundamental and clinical research

Franck Lethimonnier, Director of Inserm's Thematic Institute of Technology for Health and **Didier Samuel**, Chairman and Chief Executive Officer of Inserm

Research in biotherapies and bioproduction is at the heart of medical innovation. The transfer of these discoveries to the clinic and industry is crucial. Since 2005, Inserm and CHUs have established dedicated CICs, propelling France towards pioneering advances.

In France, around 100 research teams are working on innovative biotherapies, and a further 50 are focusing on biomanufacturing. Advances in gene editing and synthetic biology are broadening the range of possibilities. Advances in mRNA are also demonstrating their therapeutic potential.

The research is structured with clinical centers, research infrastructures, and technology research accelerators. To promote industrial transfer, "Integrators of Biotherapies - Bioproduction" have been labeled.

French research in biotherapies has progressed, with successes and innovative start-ups. Recent awareness of the importance of this field is reinforcing this momentum.

Technological research, a challenge for biotherapies and biomanufacturing

Patrick Chaton, Bernard Maillere and François Jacq, CEA

Genetic engineering and molecular and cellular engineering were at the origin of the first biomedicines - drugs produced by living cells, which are considerably more complex than the small organic molecules synthesised by chemical means - which are a useful addition to the range of therapies on offer. There are many issues surrounding these biomedicines, including aspects relating to their safety and efficacy, which are assessed during the clinical phases. But there is another dimension that should not be overlooked, namely the contribution made by technological research (TR), which helps to find new biomolecules and support their development and industrialisation processes, so that they can be made available to as many people as possible. TR organisations are therefore key players in the innovation ecosystem in an area where sovereignty is at stake.

The french landscape

Industrial biomanufacturing in France

How Leem contributes to the structuring and success of the biomanufacturing sector in France

Philippe Lamoureux, Managing Director of Leem (Les Entreprises du Médicament)

Biotechnology is the main area of development of the pharmaceuticals industry. To ensure that biotherapies are available in France and that patients have access to them in the future, French production facilities and the skills of those who work in them need to be adapted. France's position on the world market will depend on maintaining a very high level of technology and improving the competitiveness of national players. Meeting the skills needs of the biomanufacturing industry involves identifying new priority training courses, adjusting to new regulation and promoting emerging professions.

The work of competitiveness clusters

Élodie Thierion, Head of Innovation Projects - Biotech & Pharma, Medicen Paris Region, **Jessica Leygues**, General Delegate, Medicen Paris Region and **Christian Deleuze**, Chairman of Medicen Paris Region

The biomanufacturing of innovative therapies is a strategic priority for our national and European health sovereignty. If we want to achieve our objectives by 2030, be one the leading countries, it is vital to structure the biotherapy and biomanufacturing sector at various scales: regional, national, and European. The role of a competitiveness cluster like Medicen Paris Region is to foster the emergence and development of innovative health projects, by facilitating collaborations between

the various players in the sector and supporting their growth. Regionally, the cluster stimulates the innovation dynamics of the sector in connection with institutions. The fact that the clusters have joined forces within the ENOSIS Santé alliance, as well as strong relations with clusters such as Polepharma, co-organiser of the France Bioproduction Congress with Medicen, means that national actions are consistent and aligned with the priorities of France 2030. The European Council of BioRegions brings together bioclusters to promote the European sovereignty and resilience of the sector, following the example of the Bioman4R2 project.

What role for academic research and innovation in the field of biotherapies and their bioproduction? Presentation of the Priority Research Programme and Facilities (PEPR) Biotherapies and bioproduction of innovative therapies

Cécile Martinat, Inserm Steering Committee for the Programme and Priority Research Facilities (PEPR) Biotherapies and bioproduction of advanced therapies, **Anne Jouvenceau**, Coordinator of the Biotherapies and bioproduction of advanced therapies acceleration strategy of the French Agency for Innovation in Health and **Christophe Junot**, Co-pilot for the CEA of the PEPR Biotherapies and bioproduction of advanced therapies and Director of Research at the CEA

This article presents the Biotherapies and biomanufacturing of innovative therapies Priority Research Program and Equipment (French acronym: “PEPR”), which represents the upstream phase of the national Biotherapies and biomanufacturing of innovative therapies strategy. Its aim is to help position France as a major international player in this field, by facilitating the transition from academic research to innovation and prototyping. Led by INSERM and CEA for a 7 year period, with a budget of €80 million, the PEPR aims to unite the national public research community in close liaison with industrial and hospital players, focusing on two key areas: (i) the technological challenges associated with the production and deployment of current biotherapies and (ii) preparing future innovative biotherapies by developing their production methods.

Investing in innovation and biotech

Challenges and Opportunities in Biotherapies and Bioproduction - an EIB Investment Perspective

Laura Piovesan, Director General, Deputy Head of Projects Directorate, European Investment Bank, **Cristina Niculescu**, Senior Life Science Specialist and **Valeria Iansante**, Life Science Specialist

The field of biotechnology is characterized by rapid advancements and breakthrough innovations. This dynamism poses unique challenges. The need to keep up with technological advancements, regulatory requirements, and shifting market dynamics demands substantial financial commitments and a forward-thinking approach. Although investment in advanced therapies has reached a record high of over $20 billion/year in 2020 and 2021, venture capital investment in biotech declined by 30-40% in 2022. Given the sector’s strategic importance, the European Investment Bank (EIB) is committed to playing a major role in developing a resilient and zero-emission biotechnology and bioproduction industry. The Bank is supporting the field with a holistic approach across the entire value chain, from raw material supply to research, development and bioproduction. The EU bank is the biggest venture debt provider to the life sciences sector in Europe with a portfolio of over €2.7 billion, supporting more than 100 innovative companies, almost half of which are in the biotechnology space.

Innovation and technology transfer from public research: Inserm Transfert, a strategy focused on international competitiveness and long-term vision

Pascale Augé, Chairman of the Executive Board of Inserm Transfert

In the domain of biotherapies and bioproduction, the technology transfer from public research to industry holds paramount significance. This article elucidates the pivotal role undertaken by Inserm Transfert in facilitating this intricate process. By elucidating tangible and notable examples of success, it delves into the pivotal stages of technology transfer, ranging from the identification of promising breakthroughs to the realization of innovation potentials. Collaborations with the industry and dedicated support for start-ups are central components, providing insights into the ever-evolving ecosystem that shapes the future of medical treatments.

Plasma-derived antibodies, vaccines and infectious diseases, and therapies

Sanofi rises to the challenges of biomanufacturing

Jacques Volckmann, Vice President R&D France, Sanofi

Sanofi is the French leader in biomedicines, both in terms of production capacity and the wealth of therapeutic modalities marketed or under study in a wide range of fields: oncology, immuno-inflammation, neurology.

The company’s commitment to biomanufacturing is based on the long-standing expertise of its Vaccines business unit, combined with accelerated acquisition and in-house development of original therapeutic modalities, to make biologics one of the Group’s growth pillars.

This strategic shift, which began in the 2000s, has required and continues to require a response to the many scientific, technological and organisational challenges associated with the specific nature of life-based medicines. Sanofi has been able to provide initial responses to these major challenges, and continues to invest, innovate and diversify its approaches throughout the value chain.

As a national benchmark, the laboratory is helping the entire sector to achieve ever greater excellence and competitiveness, for the benefit of the healthcare system and patients. Against this backdrop, strengthening collaboration between public and private bodies is one of the keys to unlocking the synergies needed to accelerate the deployment of industrial capacity in the biotechnology field, with the aim of making France Europe's leading player in the sector by 2030.

Moderna's messenger RNA: a therapeutic revolution

Stéphane Bancel, CEO of Moderna

Moderna is one of the precursors of mRNA, a medical technology on which it has been working for over 10 years, with 43 programmes today, 34 of which are in the clinical trial phase. Over the next five years, Moderna plans to launch up to 15 new products addressing significant unmet medical needs.

mRNA is a therapeutic technology that instructs cells in the human body to produce a protein to fight a pathogen in a vaccine, before being rapidly eliminated by the body.

Biomedicines derived from plasma and therapeutic proteins: challenges and prospects

Herbert J. Guedegbe, Managing Director of LFB Biomanufacturing, **Ludovic Burlot**, LFB Biopharmaceutical Development Director and **Patrick Delavault**, Executive Vice-President, Scientific, Medical & Regulatory Affairs LFB, Member of the French National Academy of Pharmacy

Biological medicinal products derived from plasma and therapeutic proteins are a particular class of biomedicines that are relatively unknown, despite their applications in the treatment of rare and often serious diseases such as genetic diseases, cancers and inflammatory diseases. The industrial manufacturing processes involved, from fractionation to biosafety of plasma and the production and purification of recombinant proteins, are described in this article. Although these two types of biomedicine differ mainly in terms of their production source and upstream processes, the issues at stake remain comparable and often relate to questions of health sovereignty and France's strategic positioning in a context of strong competition in the rapidly growing global market for biological medicinal products.

Strategies in the fight against infectious diseases: the role of ANRS | Emerging infectious diseases

Erica Telford, Fabrice Porcheray, Sandrine Halfen, Armelle Pasquet, Nicolas Pulik, Marion Fanjat, Hervé Raoul and **Yazdan Yazdanpanah,**
ANRS I Emerging infectious diseases

The Covid-19 pandemic has stressed the need to anticipate global health emergencies. The ANRS I Emerging Infectious Diseases, a merger from the ANRS (Agence Nationale de Recherche sur le SIDA) and the REACTing consortium (REsearch and ACTion targeting emerging infectious diseases), has been created in this context. It is an autonomous agency of Inserm that leads, evaluates, coordinates and finances research on HIV/AIDS, viral hepatitis, STDs, tuberculosis and emerging and re-emerging infectious diseases.

The agency's strategy is interconnected with a comprehensive framework of initiatives implemented at national and international level, ranging from basic research to R&D and bioproduction, to improve preparedness and response to epidemics. Aspects related to innovation, societal challenges, as well as international collaboration are particularly reinforced to meet these objectives.

Viral vectors in cancer immunotherapy

Éric Quéméneur, Chief Scientific Officer, Transgene

The unique features of viral vectors have made them essential in gene therapy or for the engineering of advanced cell therapies. Their direct us as drugs in cancer immunotherapy, either as oncolytic vectors, or as therapeutic vaccines, still requires extensive research and development. The approval of T-Vec by FDA and EMA in 2015 was a booster for the field of oncolytics, and more than 20 new products are currently in clinical trials. Non replicative viral vectors have benefited from the resurgence of antitumor vaccine, and the progress of neoantigens. Both classes of viral vectors combine well with other cancer treatment modalities. The sector is very active in terms of technological and clinical innovation. This report also addresses the challenges facing viral vector-based immunotherapies to become a recognized and industrially mature therapeutic class.

Biomanufacturing cell therapies: the case of CAR-T cells by the MEARY platform

Jérôme Larghero, Professor at the Faculty of Medicine, Université Paris Cité, Director of the Department of Biotherapies at Hôpital Saint-Louis, **Stéphanie Decoopman**, Deputy Director General of AP-HP and **Philippe Menasché**, Cardiac surgeon at Georges Pompidou European Hospital and head of an Inserm team

France ranks second in Europe for the production of biological drugs, which account for a growing share of the global pharmaceuticals market. Preserving France's leadership in this field means reconciling ethical, technological, financial and regulatory issues. France has a number of strengths in this highly competitive sector, but it still needs to develop an industry to ensure the transition between R&D work, clinical trials and the industrialisation phase, and to expand its production capacity. The MEARY Centre, dedicated to the manufacture of cell and gene therapy drugs, on the site of the Saint-Louis Hospital of the Assistance Publique - Hôpitaux de Paris, can play a decisive role in transforming the excellence, know-how and disruptive technologies of our researchers and start-ups into building blocks for innovation and industrialisation. Since its creation in

2020, the MEARY Centre has aimed to facilitate the transition to the clinic by offering a simplified process. It has already developed a number of academic projects and entered into several industrial partnerships. Through this project, the AP-HP is helping to structure and drive the medical and scientific offering around the bio-production of advanced therapy drugs, as part of its overall innovation strategy.

The industrialisation of gene therapy: the example of Yposkesi

Alain Lamproye, Chief Executive Officer of Yposkesi

Gene therapy is one of the fastest growing sectors in the life sciences, with a perspective of strong evolution in the coming years. The outlook suggests that 20 of the new drugs reaching the market by 2025 will be gene therapy drugs. The industrialization of the production of these advanced therapy drugs is one of the major challenges of medicine. The market for CDMOs specialized in this field has become considerably more complex in recent years, through massive investments in new production capacities or the acquisition of existing units. The market leaders are mainly located in the US, but it is important for Europe, including France, to develop sufficient capacities to ensure the future production of these new biomedicines. The example of Yposkesi, the leading French actor, is presented in this article.

Biotherapies: drugs like any others?

The challenges of therapeutic evaluation of biotherapies: focus on advanced therapy medicinal products

Fabienne Bartoli, Director General of the French National Authority for Health, **Joachim Baba**, Scientific Project Manager, Drug Evaluation Department, Haute Autorité de Santé (French National Authority for Health) and **Salah Ghabri**, Economic evaluation referent within the Haute Autorité de Santé's Drug Evaluation Department

Therapeutic hopefuls, advanced therapy medicinal products (ITMs) differ from other conventional medicines in that they are administered as a single dose with the aim of curing a chronic disease.

In addition to the promise of a cure offered by ITMs and the often very high unit prices claimed, these drugs present major challenges for the evaluation and pricing process of the French healthcare system, as the demonstration of their efficacy is often complicated by a large number of uncertainties.

Faced with the emergence of ITMs on the French market, the French National Authority for Health (HAS), the agency responsible for granting access to reimbursement for healthcare technologies, is fully committed to assessing this type of drug in order to provide the public decision-makers concerned with the information they need.

The challenges of biotherapy pricing

Philippe Bouyoux, Chairman of the Economic Committee for Health Products and **Jean-Patrick Sales**, Vice-Chairman of the Economic Committee for Health Products, responsible for medicinal products

From the point of view of pricing, the biotherapies market currently covers several distinct situations and debates.

A flow of expensive innovations. Some of the biotherapies that have been on the market for several years now have conquered the market in large population indications, particularly in the fields of diabetes, asthma, oncology and inflammatory diseases of the joints, digestive tract or skin. Among the most recent therapies, gene therapies claim extremely high prices due to a very specific economic model linked to single administration treatment. The resulting increase in expenditure calls into question the pricing system, as laboratories adapt their strategy to the characteristics of biotherapies.

The regulation of these products over time via price cuts justified by extensions of indications, and competition between players.

The arrival of biosimilars. Since 2016, this has accompanied the ageing of the class of biotherapies and raises the question of the analogy - complete or not? - with generics.

The ethical dimension and cross-disciplinary issues

Biotherapies: opportunities and accessibility

Alain Fischer, Collège de France, Paediatric Immunology, Haematology and Rheumatology Unit, Hôpital Necker Enfants malades, Assistance Publique-Hôpitaux de Paris; Imagine Institute

Advances in biomedical research are leading to a flurry of new drugs based on biotherapies that include recombinant proteins, monoclonal antibodies, gene therapy and RNA therapy. These biotherapies are used to treat cancers, inflammatory diseases, genetic diseases as well as for vaccination. Expectations of new drugs of these classes to be developed in the years to come are great. However, these innovative drugs are marketed at very high prices, possibly jeopardizing their accessibility to the whole population. Therefore, new rules governing prices regulation need to be generated on an international ground in order to preserve an adequate balance between private interest and common good. It can also be considered to produce some of these new drugs by non-profit entities.

The ethical issues raised by biotherapies

Pierre-Henri Duée, Sophie Crozier, Florence Jusot and **Jean-François Delfraissy**, National Consultative Ethics Committee for Health and Life Sciences (CCNE)

For several years now, new drugs have been emerging from biomedical research to treat serious illnesses such as cancer and inflammatory diseases. These new therapies call on recent areas of research that break with chemical or biochemical research. They are often personalised and are particularly expensive.

These characteristics raise a number of ethical issues, starting with the question of what is a ‘fair price’ for these therapeutic innovations, and also the question of how to prioritise access to them.

The analysis presented in this article is based on the opinions of the French National Consultative Ethics Committee, in particular Opinion 135 adopted on 24 September 2020. This work also stresses the importance of establishing a general framework to regulate the flow of these new therapies and to take account of public health issues, with ethical benchmarks based on the concepts of general interest and the principle of equity. Lastly, structural changes that open up new business models would be desirable, but this will require a major cultural shift.

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