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Creating Conditions for the Success of The French Industrial Advanced Therapy Sector

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Abstract – Although the European Union merely followed the initiatives of the United States and Japan by introducing special regimes for orphan medicinal products, it has introduced a special status for a new category of biological medicinal products, advanced therapy medicinal products (ATMPs), adopting specific associated regulations. European Regulation (which constitutes the highest legal instrument in the hierarchy of European law texts) [EC] No. 1394/2007, published in 2007, uses this term to define somatic cell therapy medicinal products, tissue-engineered products, and gene therapy medicinal products, possibly combined with medical devices. The stated objective was two-fold: both to promote their industrialization and market access, while guaranteeing a high level of health protection for patients. Since publication of the regulation, few marketing authorizations have been granted in Europe, and these have not been accompanied by commercial success. However, certain recent studies show that this is a growing sector and that France remains the leading European nation in terms of clinical trials. This round table brought together a panel of representatives of French public and private protagonists from the advanced therapy sector. The discussions focused on the conditions to ensure the success of translational research and, more generally, the French advanced therapy sector. These enabled a number of obstacles to be identified, which once lifted, by means of recommendations, would facilitate the development and success of this sector.

Abbreviations: see end of article.

† Articles, analyzes and proposals from Giens workshops are those of the authors and do not prejudice the position of their parent organization.

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1. Introduction

1.1. Regulatory context

European Regulation (EC) No. 1394/2007, published in 2007, defined a new category of biological medicinal products: the advanced therapy medicinal products (ATMPs). These cover somatic cell therapy medicinal products, tissue-engineered products, and gene therapy medicinal products, possibly combined with medical devices. Until 2007, only France had such regulations. Until now, these therapeutic products were tissue or cell therapy preparations (CTP) or gene therapy preparations and were not considered medicinal products as defined in the French Public Health Code. However, they remained within the competence of the French National Agency for the Safety of Medicines and Health Products (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*, ANSM) and governed at national level based on the tissue/cell directive (Directive 2004/23/EC). They were produced by authorized establishments, which could include hospitals, *Etablissement Français du Sang* (EFS) and pharmaceutical companies, and were not governed by good manufacturing practice (GMP) guidelines for "medicinal products". Henceforth, a product for which the manufacturing process does not involve substantial modifications AND having the same purpose in the donor and recipient shall remain a cell or tissue preparation. If one of these two conditions is not fulfilled, it shall be considered an ATMP. The result is, other than conventional haematopoietic stem cell transplants and transplantation of Langerhans islets, most advanced therapy products developed in France henceforth meet the definition of an ATMP and thus have a different regulatory framework.

As ATMPs are medicinal products, they first require a marketing authorization (MA) in order to be commercially available. This falls within the scope of the centralized procedure and is granted by the European Union after evaluation by the European Medicines Agency (EMA). The production and distribution conditions for ATMPs should comply with GMP. In Europe, any establishment complying with GMP may prepare medicinal products once it has been granted pharmaceutical establishment status; however, healthcare establishments in France are not eligible for this status. ATMPs are subjected to the principle of the free movement of goods and may therefore move within the European economic area outside the country hosting the production facility, and their post-marketing surveillance falls within the scope of pharmacovigilance.

For ATMPs prepared on a non-routine basis for a given patient, and used within the same Member State, Article 28 of the European Regulation defines the "hospital exemption" which falls within the scope of a national authorization. In other words, hospital exemptions for ATMPs are not subject to the requirements of Regulation No. 1394/2007 and can not be the subject of a centralized MA application; they are covered by a national regulatory framework which should be equivalent to the applicable Community rules in terms of quality and safety.

In France, this European regulation, which is being implemented immediately in compliance with European law, led to changes in the French Public Health Code further to the publication of Law No. 2011-302 of 22 March 2011. This law was then presented in Decree No. 2012-1236 of November 6th 2012 relative to ATMPs, introducing the concept of hospital exemption defined by the term "advanced therapy medicinal products prepared on a non-routine basis" (ATMP-NR). While ATMPs are required to be manufactured in a public or private pharmaceutical establishment, or one that has been created within not-for-profit organizations other than healthcare establishments, ATMP prepared on a non-routine basis may also be manufactured by facilities within healthcare establishments.

This is the context in which new facilities dedicated to the production of ATMPs in France have recently emerged:

– on the one hand, two unique industrial production facilities in Europe:

- CELL*for*CURE, a subsidiary of LFB, for which the very large scale ATMP industrial production platform, destined for late clinical phases and the market access, was inaugurated in Les Ulis on September 10th, 2013. The creation of this platform is part of the C4C project and received support from the *Investissements d'avenir* programme and BpiFrance (formerly Oséo) in 2012. The total investment amounts to 80 million euros including support from BpiFrance for the development of 5 projects proposed by small and medium-sized businesses (SMB) and academics up to the market stage, amounting to 20 M€;
- Genethon, the French Association against Myopathies (*Association Française contre les Myopathies* [AFM])-Téléthon laboratory was awarded pharmaceutical establishment status by the ANSM on June 27th 2013. Its production centre, Genethon Bioprod, is thus authorized to produce ATMPs. Building costs for Genethon Bioprod amount to 28.5 million euros, including 5.5 million funded by the AFM, 8 million by the *Conseil Régional d'Ile de France*, 7 million by the *Conseil Général de l'Essonne* and 8 million by the *Génopole d'Evry*. Its annual operating costs (approximately 10 million euros) are fully financed by the AFM thanks to Téléthon donations.

– These industrial facilities have now been extended to:

- public protagonists such as *Etablissement Français du Sang* (EFS) and *Etablissement de Santé des Armées*. As regards EFS, Atlantic bioGMP (ABG), located close to Nantes, was awarded pharmaceutical establishment status on 6 February 2014, for its ATMP production activity. In terms of funding, EFS, *Nantes Métropole*, *Conseil Régional de Pays de la Loire*, *Conseil Général de Loire Atlantique* and the European Regional Development Fund (ERDF [European Union]) contributed an investment of 5.2 million euros. ABG operating