Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Response
on the public consultation on the regulation on advanced therapy medicinal products

The French National Institute of Health and Medical Research (Inserm) is a public scientific and technological institute, which operates under the joint authority of the French Ministry of Health and French Ministry of Research. Inserm encompasses more than 3,000 employees and 1,000 of research groups in partnership with the University, most of them being established in University hospitals and among which hundred are dedicated to gene or cellular therapies. As the only French public research institute to focus entirely on human health, Inserm supports the development of research infrastructures in the field of public health and clinical research, particularly large health studies and clinical investigation centres; this implies fostering translational approaches and encouraging teams of different disciplines to unite around these infrastructures. Eight of them are dedicated to advanced biotherapies.

Over the past five years, Inserm has sponsored 10 clinical trials based on advanced therapy medicinal products.

The following document is the outcome of the experience as an academic sponsor and the experience of the clinical investigation centres dedicated to advanced biotherapies.

Consultation topics :

2.1 Marketing authorization application requirements for advanced therapy medicinal products:

We agree that the quality, efficacy and safety of the medicinal products for advanced therapies have to be demonstrated in order to ensure patients safety and to support their marketing.

However we would like to point out that:

- most of the advanced medicinal products concern individual patients and requirements should take into account the medical status of the patients with regards to the benefit/risk ratio; thus specific requirements should be proposed, keeping in mind that marketing authorization are rarely considered.
- however, if the product demonstrates a larger interest and evolves towards a marketing authorization, clinical trials for individual patients conducted under the auspices of less extensive

requirements must be taken into account for future developments; in this case, extended pre-clinical studies might be required to achieve the requirements for marketing authorization.
-preclinical models are not always available or pertinent as recently reported (Seok et al, PNAS, February 26, 2013, vol. 110, no. 9, 3507–3512)

2.2 Requirements for combined advanced therapy medicinal products :

Numerous combined advanced therapy medicinal products including medical devices are under development. We consider that these products should be evaluated in the same way and with similar requirements that simple advanced therapy medicinal products.

2.3 Hospital exemption :
Hospital exemption is an important issue.

In France, most of innovative therapies are developed in public and academic hospitals and mainly concern phase I/II clinical trials and are prepared for individual patients. In addition, numerous clinical trials are carried out using autologous cells or MHC-matched allogeneic cells. The development of individual preparations for patients belongs to the field of the clinical research and even if most of these trials will not go up to the market, they clearly contribute to the scientific and medical progress and to translational research from bench to bedside and vice versa.

We think that this hospital exemption must be maintained and should provide enough flexibility to favour innovative therapies:
- Specific guidelines should be edited for products preparation taking into account that these products, derived from viable organisms (cells for instance), are not sterile (patients being not sterile) and not standardized. Thus, the LD1 from GMP guidelines, applied to sterile products, is not always appropriate.
- Guidelines must be flexible allowing for risk analysis of each product and not on fixed obligations.
- These specific guidelines should permit, as previously indicated, that products prepared in a context of hospital exemption could evolve towards ATMP with marketing authorization.
- In France, the delivery of medicinal product is possible only under the responsibility of a pharmaceutical facility (“Etablissement Pharmaceutique”). Only one Institution (AP-HP, hosting all the public hospitals within the Paris municipality) includes such a facility. This represents an important inequality with other European countries for hospital exemption. This point should be clarified by taking clearly into account that advanced therapy medicinal products are biological products and not drugs.

- INSERM, as a public research institution, is particularly concerned by hospital exemption because of the Clinical Investigation Centres for Biotherapies (CIC-BT) that are mixed structures between INSERM and public academic hospitals created to develop innovative ATMPs.
- Thus, hospital exemption for academic hospitals is important to maintain a strong link between research, translational medicine and medical progress including the creativity of innovative therapies. Today, industry cannot provide such environment, expertise, know-how and services
Overall, we think that maintaining hospital exemption will be more than important.

2.4 Incentives for the development of advanced therapy medicinal products :
We find it very important to maintain several incentives to support the development of these innovative products, reduced fees and scientific advices
Furthermore, incentives should take into account:
- that requirements for marketing authorization are extensive and very expensive. It is particularly the case for animal models in order to evaluate toxicity, carcinogenesis or bio-distribution. We find

that incentives should include the certification and support of laboratories involved in these fields to increase the studies relevance and to reduce costs.
- translational research should be considered more specifically and supported through specific fundings.

2.5 Scope and adaptation to technical progress :

The field of embryonic stem cells as well as induced pluripotent cells should be considered with specific attention.