Response to the European Commission public consultation on the Regulation on Advanced Therapy Medicinal Products

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We form a group gathering all the hospital-based laboratories that manipulate, store, and manufacture advanced therapy medicinal products (ATMPs) in France. As major contributors to the development of Advanced Therapy Medicinal Products (ATMP) in France, we assessed the impact of European Regulation No 1394/2007 and related Directives on the development of ATMPs by our facilities.

Consultation topics :

2.1 Marketing authorization application requirements for advanced therapy medicinal products:

We agree that the quality, efficacy and safety of ATMPs have to be demonstrated in order to ensure patient safety and to support a marketing authorization.
However we would like to point out that most of the ATMPs developed by academia (like somatic cell therapy product and gene therapy products) concern individual patients, in Phase I/II clinical trials (investigational trial) receiving individually-tailored products rather than reproducible therapies produced as batches and marketing authorization are rarely considered at this stage of development. Furthermore preclinical model, required for marketing authorization are not always available or pertinent. Thus, for investigational clinical trials authorization, requirements should take into account this peculiarity as well as the medical status of the patients with regards to the benefit/risk ratio and specific requirements should be proposed, for example, based on clinical investigations published in the literature or issued from data banks or first-in-man compassionate use cases previously performed.
If the product demonstrates a larger interest (proof of concept and efficacy of the product clearly demonstrated) and evolves towards a marketing authorization, investigational clinical trials for individual patients conducted under the auspices of these specific requirements should be suitable for future development, based on clinical outcome and adverse event data during the trial, in place, or combined if necessary, with extended pre-clinical studies.
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2**.2 Requirements for combined advanced therapy medicinal products** :

Numerous combined ATMPs that include medical devices are under development. We consider that these products should be evaluated in the same way and with similar requirements as simple ("non-combined") ATMPs. With this aim, the definition of these "combined products" needs to be clarified: for example would "cells and medical devices combined out of GMP facilities (in surgery facilities for example), be considered a combined ATMP? Also, the role of medical device, only as cells support or inducing modifications of key cell characteristics (for example cytokine secretion or immunological functionality of the cells) could modified the classification?

2.3 Hospital exemption:

Hospital exemption is an important issue and definitions of the Hospital Exemption Clauses need clarifications

In France, Academic Institutions are contributing to the development of most of ATMPs. These ATMPs involve mostly Phase I/II clinical trials and are prepared for individual patients. The development of individual preparation for patients belongs to the field of the clinical research and patient care; hospital exemption is the source of Innovation. It is important to maintain a strong link between research, translational medicine and medical progress including the creativity of innovative therapies and this is supported by academic groups. Even if some of these trials will not reach the market, or did not intend to support a marketing authorization dossier, they clearly contribute to the scientific and medical progress and to translational research from bench to bedside and vice versa. In addition, pharmaceutical manufacturers have no interest and do not want to support the early phases of validation for cell and gene therapy products (Phase I / II) considered as a proof of concept where safety and efficacy have not been demonstrated. Finally, ATMPs prepared in the context of hospital exemption are high quality products.

Proposals:

- The conditions for application of the hospital exemption need an unified definition.
- The interrelationship between hospital exemption and clinical trials needs also clarifications. The data arising from clinical trials in the context of hospital exemption should be used as part of the investigational medicinal product dossier for subsequent clinical trial applications and marketing authorizations.
- Guidelines should be flexible, based on risk analysis methods and not fixed on obligations only. Particularly, we consider that the LD1 from GMP guidelines, applied to sterile chemical products, for large scale industrial preparations is not always appropriate for our preparations. For exemple, most of them , in closed systems or in controled environment do not require permanent records of particules or extensive gelose contact to record microbiolgical risk. In the experience of french academic GMPs , on >700 ATMPs prepartions in the environment required by the previous European Regulation No 2004/23/CE and related directives no bactericidal contamination was observed. In contrast, some contaminations were detected in the harvest products. Moreover, these systems can induce adverse event -

Specific GMP guidelines should be proposed for ATMPs preparations taking into account that therapy medicinal products are biological products that cannot be assimilated to pharmaceutical drugs.

Special terms in France-

- "Public Health Code": In France, the manufacturing of medicinal product is limited to pharmaceutical Establishments ("établissement pharmaceutique"). The aim of this terms is to avoid medicinal marketing between, or inside, hospitals. Thereby, therapy cellular unit from hospital are not authorized to deliver ATMPs. This fact represents an important inequality with other European countries. French hospitals should obtain, from European regulation, the rights to deliver ATMPs with no commercial purpose.
- French health authorities propose a distinction between autologous and allogeneic ATMPs for hospital exemption. We consider that allogeneic ATMPS should also benefit of hospital exemption if they respond to the definitions "for individual patients in the absence of a marketing authorisation ».This point needs to be clarified.

So the hospital exemption must be maintained and should provide enough flexibility to favor the development of innovative therapies regardless of the type of ATMP.

2.4 Incentives for the development of advanced therapy medicinal products :

The incentives to support the development of these innovative products, reduced fees and scientific advices are essential.

These incentives should take into account that requirements for marketing authorization are extensive, include considerable bureaucratic requirements and are very expensive to meet, particularly quality controls and animal models by GMP certified laboratories. Only large pharmaceutical companies are equipped to respond to these requirements while a great proportion of ATMPs are not pioneered by industry but by local academic groups of clinicians, scientists and cellular therapy units.

In addition, we suggest:

– that the 90 % reduction in fees for scientific advice or respond to requirements that supports transition from academia to industry are not restricted to SME but extended to hospitals and other not-for-profit academic institutions.

- the labeling and support of academic GMP certified laboratories involved in quality control, toxicity, carcinogenesis or biodistribution evaluation to increase the preclinical studies relevance and reduce costs.
- specific funding for translational research in the field of ATMPs.

2.5 Scope and adaptation to technical progress:

The field of embryonic stem cells as well as induced pluripotent stem cells should be considered with specific attention. We suggest adding a requirement that the quality controls and preclinical investigations be precisely analyzed and confirmed by independent experts, prior to submission in clinical trial applications or marketing authorization applications.