Comments of the Frennch Society for Cell and Gene Therapy (STFCG)
on the public consultation on the regulation of advanced therapy medicinal products (ATMP)
31 /03 /2013

A public consultation paper on the regulation of advanced therapy medicinal products has been sollicited by the Health and Consumers Directorate General of the European Commission, to seek the opinion of stakeholders and to prepare the commission report on the application of the Advanced Therapy Regulation.
There are five topics of consultation :
1. Marketing authorisation application requirements for advanced therapy medicinal products.
2. Requirements for combined advanced therapy medicinal products.
3. Hospital exemption.
4. Incentives for the development of advanced therapy medicinal products.
5. Scope and adaptation to technical progress.

As an active member of the research and clinical community aiming to develop new products for gene and cell therapy for human inherited and acquired diseases, the French Society for Cell and Gene Therapy (SFTCG) recognizes the importance of this consultation and acknowledges the effort being made by the EC to advance the field and the regulatory aspects of cell and gene therapy.

The goal of the SFTCG is to promote basic and clinical research in gene and cell therapy, by promoting education, exchange of information and technology and by serving as a professional adviser to stakeholder communities and regulatory bodies in Europe. Towards that goal, the SFTCG is strongly committed to support scientists and clinicians involved with basic and translational research on gene transfer and clinical applications of gene and cell therapy with a close attention to regulatory aspects. The society has always been active in interacting with other societies and regulatory bodies at the national and EU level to improve knowledge and to facilitate the development of gene and cell therapy applications.

As we are now experiencing significant progress towads clinical applications in the field of gene and cell therapy, we must commit to a continued revision of the regulatory framework for preparing and conducting clinical trials and for developing new medicinal products. This is a challenge from the scientific and regulatory view points and a key action for our Society. We are committed to work, in close collaboration with Regulatory Authorities, to update the requirements and to overcome the roadblocks imposed by conventional preclinical testing methods when they do not apply with the specific design and requirements of gene and cell therapy products.

**Specific responses to consultation topic : The SFTCG board wishes to make several comments**

**2.1. Marketing authorisation application requirements for advanced therapy medicinal products.**

In order to facilitate the translation of scientific research into clinical applications leading to the development of new cell and gene therapy medicinal products forhuman health, our Society advocates a revision of regulations that could reduce unnecessary complexity, long delays and high costs without compromising the quality standards and safety to patients.

Often, a distinction is made beetwen ATMPs that are commercially viable, will go to MA and usually concern frequent acquired diseases, such as cancer, and those ATMPs that concern personalized medicine or rare diseases and that are more restricted in their potential market sizeand commercial value. Yet, these two categories of medicinal products can sometimes become intertwined. Indeed, marketed products such as epigenetic modifiers used in cancerology might become useful to treat some rares diseases and inversely, gene therapy vectors developed for rare disease applications migh become useful to treat cancer or infectious diseases. Nevertheless, many ATMPs that are developed in the context of specific and rare applications without commercial market might offer remarkable promises for therapeutic benefit, scientific knowledge and societal impact and we believe that their development should be facilitated.

Advanced Therapy Regulation should facilitate first-in man studies in limited patient groups by facilitating the preclinical development and the administrative procedures involved without impairing the quality requirements of the clinical product or the ethical principles involved. In that sense, it would be beneficial and ethical to allow and to encourage sharing information issued from such small-scale studies in man, within the scientific, biomedical and regulatory community. Results of preclinical and clinical data could be shared by investigators using very closely related protocols or similar gene and cell therapy tools (for example specific types of gene delivery vectors). For instance, high quality biosafety of biodistribution studies with well-described preparations of GMP vectors or with well-characterized preparations of cells could be shared whenever possible, to limit the conduct of similar costly and time-consuming preclinical studies. Results of clinical investigations could be rapidly communicated and registries of small studies made available. This would be particularly valuable and practical in the field of rare diseases for which a limited number of patients and therefore a limited amount of clinical data are available.

In these cases, the requirement for extensive preclinical data and particularly data obtained in small animal models that are sometimes poorly relevant (not predictive in term of toxicity and efficacy) should be considered by regulatory agencies with more flexibility. Publication of negative results, often important for the design of new products or protocols, should be encouraged. Human induced pluripotent cells are for example now emerging as potent models to test drug toxicity and efficacy in a human context. Such cell lines could become validated standards in the field.

Many ATMPs rely on patient- or donor-derived tissues for which there is great variability. Thus a formal definition of ATMPs seems difficult in many cases. Thus, more flexibility is

recommended in the definition of the Medicinal Product than currently exists and that is accepted for conventional medicines obtaining MA.

**2. Requirements for combined advanced therapy medicinal products.**

There is a need to harmonize the definition of gene and cell therapy products, including what constitutes a combined ATMP, across Member State of the EU to avoid heterogeneity in the development of these ATMP and to facilitate submission of the product to EMA for centralised marketing authorization.

**2.3 Hospital exemption**

We acknowledge that hospital exemption (HE) is a potentially important step in the development of an ATMP. However, there is a need to standardize conditions and requirements for HE and the use of first-in-man clinical data for further clinical development, across EU countries. All national regulatory agencies and ethical committees within Europe, should strive to apply similar basic standards for approval of clinical trials whether they are local, national or at the European level. These standards should be based on thorough and rationale evaluations of risk benefice. HE is useful to permit the development and validation of ATMPs when no other alternative treatment is available. However a systematic use of HE raises ethical issues. HE studies should be performed with the highest possible quality standard. Harmonized regulation between member states could warrant the rationale and safety of the ATMP and the conditions of authorization.

Such conditions of authorization would potentially help the use of data arising from these first-in-man cases as part of the investigatory medicinal product file for subsequent clinical trial applications (« phase 0 »), to reinforce or even replace pre-clinical animal studies.

In an ethical perspective, a registry for these HE data would be important, to ensure the quality of these first-in-man ATMP use and the upcoming availability of obtained data for subsequent clinical trials .

**4. Incentives for the development of advanced therapy medicinal products.**

There is a gap to fill between ATMP that are commercially viable and will go for MA and those that are not . In that respect, Advanced Therapy Regulation should facilitate the development of academic and non-profit intermediate flexible structures able to develop and manage ATMP for the treatment of rare diseases for which there is less interest from industry, while garantying the quality of the product.

**5. Scope and adaptation to technical progress.**

First in man proofs of concept and phases I-II trials remain mostly led by academic structures These academic structures have a major role to play in the development / reassessment of EU legislation in this field. Standardization and simplification of the

regulation and authorizations and facilitation of these early steps in man by academic stakeholders should be a priority.

Biotherapies are an extremely rapidly moving field where technics and tools improve very rapidly. For example, ex vivo gene transfer techniques or even the targeted delivery of a viral vector using sophisticated specific surgery could hopefully be replaced in the near-future by simple intravenous delivery of improved targeted vectors, thus simplifying delivery protocols but radically modifying the nature of the Medicinal Product, its preclinical requirements in term of safety and tolerance. Clinical laboratories may soon benefit from widely available deep DNA sequencing technology that could potentially revolutionize preclinical toxicology or patient safety monitoring. All stakeholders who participate to the development of the EU legislation should take into account that these major modifications would benefit from rapid and flexible adaptation /reassessment of the regulation to facilitate the development of these new ATMP.