PUBLIC CONSULTATION PAPER
ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

2.1. Marketing authorisation application requirements for advanced therapy medicinal products.
The Advanced Therapy Regulation provided for adapted requirements in terms of the dossier that applicants must prepare to demonstrate the quality, efficacy and safety of the medicinal products when applying for a marketing authorisation.
The amount of data that must be generated for the submission of a marketing authorisation application is critical to ensure a high level of public health protection. Proportionality of the requirements is also important to facilitate the marketing of advanced therapies.
Please provide your comments on the requirements for marketing authorisation applications set out in the Regulation.

The submission of a Marketing Authorisation Application (MAA) for ATMPs must demonstrate the high quality of non-clinical and clinical data to be included in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and justify any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC as amended by Directive 2009/120 EC.

The Advanced Therapy Regulation states that "(13) Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, technical requirements, in particular the type and amount of quality, preclinical and clinical data necessary to demonstrate the quality, safety and efficacy of the product, may be highly specific. While those requirements are already laid down in Annex I to Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they need to be established for tissue engineered products. This should be done through a procedure that provides for sufficient flexibility, so as to easily accommodate the rapid evolution of science and technology."

EURORDIS supports the application of flexible approaches to accommodate the high specificity of ATMPs while preserving high quality standards for the ultimate benefit of patients.

The "risk-based approach" is based on the identification of various risks associated with the clinical use of an ATMP and risk factors inherent to the ATMP with respect to quality, safety and efficacy and its concept has been introduced to the legislation with the revision of Annex 1, part IV of Directive 2001/83/EC as amended by Directive 2009/120 EC. **Currently, the application of the risk-based approach in the preparation of a MAA dossier is optional. In our opinion a more compelling and structured framework for its adoption for MAA should be envisaged since we believe that it would facilitate both product development and assessment process** (see Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products).

2.2. Requirements for combined advanced therapy medicinal products.
The existence of advanced therapy medicinal products that incorporate one or more medical devices has been recognised and regulated in the Advanced Therapy Regulation. In particular, combined advanced therapy medicinal products are to be authorised by the Commission following the scientific assessment of the European Medicines Agency. The applicant must demonstrate that the essential requirements of the specific legislation on medical devices have been complied with and there is a possibility for the Agency to consult the relevant notified bodies.
No application for a combined advanced therapy medicinal product has been submitted to the European Medicines Agency yet.
Please provide your views on the authorisation procedure foreseen in the Advanced Therapy Regulation for combined advanced therapy medicinal products.

No current views concerning this consultation item.

Hospital exemption
The Advanced Therapy Regulation empowers Member States to authorise the use of advanced therapy medicinal products in hospitals for individual patients in the absence of a marketing authorisation. The so-called hospital exemption provides for flexibility to address the situation of individual patients; however, a too large application of this exemption may discourage the application for marketing authorisations.
Please provide your views on the application of the hospital exemption.

Article 28 of EU Regulation 1394/2007 fixed the criteria on the exemption of ATMP from the central authorisation requirement. These products are prepared on a non-routine basis, according to specific quality standards equivalent to centralised marketing authorisation, and used in a hospital within the same Member State (MS) in accordance with a medical prescription for an individual patient, the so-called hospital exemption (HE). MSs are required to implement this community requirement for a HE by putting in place the guidelines at national level to meet the specific requirements of the Regulation.

EURORDIS supports HE as a tool to offer individual patients a customised, innovative and safe ATMP ensuring that relevant community rules to quality and safety are respected.

Authorisation of an ATMP through the HE is under the exclusive responsibility of the National Competent Authorities that have to follow the legal implementation of HE in a specific MS.

In EURORDIS' view HE should not considered a way to escape regulatory control, to create two different quality standards or to bypass the generation of valid clinical data. HE should be viewed as a complementary and harmonised European regulatory approach, suitable for ATMPs that answer primarily to patients' urgent needs, for ATMPs not eligible for MA and for ATMPs developed by academic groups, which may otherwise be lost for the lack of resources and interest.

We would like to emphasise that HE must ensure consistent and appropriate quality and safety standards of manufacturing process for ATMPs across Europe, to facilitate treatment and foster innovation while at the same time preventing misuse of ATMPs.

HE is a powerful tool that is in the spirit of innovation and thus the ATMP legislation however it must be used with caution and responsibility in particular when approved ATMPs with EU centralised procedure exist.

To increase transparency and consistency of HE in Europe we suggest:

- **Collection of all official text from EU MSs referring to the implementation of HE, analyse them for their consistency with the initial spirit and words of the EU Regulation ATMP, identify the common points and differences, propose a technical reference text with a set of good / best measures identified from MS and finally encourage MSs to update/ revise their national official implementation texts according to this technical guidance based on optimal implementation from other MSs. This approach would enhance consistency across MSs while supporting a more stringent application of HE**
- **Creation of a centralised database or registry on HE and relative outcomes in order to encourage further development of ATMPs towards a central MA to make these innovative treatments available for all eligible patients in Europe.**

2.4. Incentives for the development of advanced therapy medicinal products.
Advanced therapies are at the cutting edge of innovation. The full development of the potential of this sector is closely linked to the evolution of scientific knowledge. The Advanced Therapy Regulation provides for a number of incentives to support the development of these products, such as certification for quality and non-clinical data, reduced fees, scientific advice.
Please provide your views on the incentives provided for under the Advanced Therapy Regulation.

The Regulation (EC) No 1394/2007 on ATMP contains the Chapter 6 with 4 articles on incentives. The article 16 on Scientific Advice (SA) provides a 90% fee reduction for small and medium enterprises and 65% for other applicants. From our point of view the SA fee reduction is an important incentive to encourage the early dialogue with the developers of ATMP that are frequently academia or charity and need greater support to finalise the further development of innovative products.

For this reason we propose to provide a 90% fee reduction for academia and charity so to align it with SMEs and encourage development of ATMP by the stakeholder category which has the highest potential.

The certification procedure for quality and non-clinical data¬ according to the Article 18 of Regulation (EC) No 1394/2007 represents a further potential incentive for the development of ATMPs, which is currently restricted only to SMEs.

Although EMA has produced a guidance document for the ATMP certification procedure to explain the scope of the incentive encouraging the application of SME, the results after 5 years of implementation have been very poor.

The main reason for the failure of the certification could be ascribed to the lack of a clear scope, value or benefit of the certification as perceived by SME.

EURORDIS suggests two initiatives to improve the scope and value of certification for ATMPs:

- **We are convinced that certification for ATMP on quality and non-clinical data could be a strong incentive if it was combined with the concept of market exclusivity when the developers reach the market. Two situations could be considered:**
    - **A 2 year extension for Market Exclusivity of an ATMP designated as Orphan Medicinal Product, similarly to the Market exclusivity extension provided to OMPs for which paediatric studies have been performed. and**
    - **1 to 3 years MA exclusivity for other ATMPs that are not intended for rare conditions, so as to provide an additional stimulus in investing in ATMP**
- **the Certification should be extended to academia and charities. This would be a true benefit for research institutions and a clear value facilitating partnership with biotech or pharmaceutical companies to take forward the product development, regulatory process and commercialisation, or, to transfer the potential ATMP to a for profit company**

  In this case the Certification would be more attractive for the developers therefore increasing the research interest and stimulating competition on issues of quality and safety that currently represent the primary gaps responsible for the development or failure of ATMPs.

2.5. Scope and adaptation to technical progress.
The Advanced Therapy Regulation applies to gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products.
Please provide your views on the scope of the Regulation and in particular as to whether the scope should be modified to take account of technical progress.

None for this consultation item.