REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Pfizer Feedback to the European Commission on the Public Consultation Paper

INTRODUCTION

Pfizer welcomes the opportunity to comment on the regulation on advanced therapy medicinal products in Europe. The European Commission's interest in the practical implementation of the regulation is timely in this rapidly developing area.

Pfizer is developing Advanced Therapy Medicinal Products (ATMPs) working with research establishments as well as small and medium-sized enterprises (SMEs) in the early clinical development of potential gene therapies and cell based therapies. As regulation and guidance developments we would encourage agreement on requirements for ATMPs among European member states, at a European and international level.

Although general requirements for ATMPs are similar between international regions, we would encourage discussion on areas of conflicting requirements where these may form barriers to marketing of medicinal products. One potential area for investigation would be the applicability of the US limitations on cell and tissue products sourced in Europe to allogenic stem cell therapies.

Pfizer's comments relate to two main areas:

1. Requirements for traceability as defined in Article 15.1 are too broad, placing a significant and unnecessary burden on industry. Guidance from the Commission foreseen in Article 15.7 would be helpful in clarifying the interpretation of the requirements.

2. In any update of the regulation there is opportunity to encourage interaction between innovators and regulatory authorities at the complex early stages of ATMP development. This might be through an extension of the certification available under Article 18 or through provision for certification of an ATMP active ingredient file.

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.

Pfizer Comments

Article 15 of Regulation 1394/2007 deals with requirements to maintain traceability systems. We support the requirement in Article 15.2 for traceability linking of each product to the patient who received it and *vice versa*. However, for Article 15.1, we feel it is an unnecessary burden on marketing authorisation holders to maintain a traceability system for all substances coming into contact with cells or tissues. The requirement to consider all substances serves no public health interest as, if interpreted broadly, would needlessly include traceability of such substances as pipettes, incubation flasks and the water used for incubation solutions. We suspect the intention of the requirement was to ensure the traceability of substances that may affect product quality or safety (such as materials of biological origin).

Additionally, given the definition of starting and raw materials in Annex I to Directive 2001/83/EC, we believe clarification is needed on the interaction (if any) between traceability requirements for marketing authorisation holders and traceability requirements for tissue establishments (defined in 2004/23/EC and its implementing Directive 2006/86/EC). We note that in Annex VI.A of Directive 2006/86/EC product identification is limited to at least the 'description and origin of the products, processing steps applied, materials and additives coming into contact with tissues and cells and having an effect on their quality and/or safety'.

We look forward to the guidelines on traceability requirements foreseen in Article 15.7 of Regulation 1394/2007. We would recommend that the traceability requirements for marketing authorisation holders are limited to operations outside the scope of Directive 2004/23/EC, perhaps to manufacturing processes occurring after the establishment of a Master or Working Cell Bank. The scope should be limited to substances coming into contact with cells or tissues that affect product quality and/or safety. Such a requirement may complement the Good Manufacturing Practice requirements for batch processing records.

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.

Pfizer Comments

Article 7 of Regulation 1394/2007 describes medical devices, bio-materials, scaffolds or matrices. While we agree that it is useful to require details on these materials in accordance with Annex I to Directive 2001/83/EC, this does not mean that such components automatically require CE marking in Europe as Medical Devices (under Directive 93/42/EEC). We consider medical devices are components with a distinct medical function within the combination product (such as stents). The terminology of 'scaffold or matrices' should reflect materials supporting the administration of the active material (the advanced medicinal product). Scaffold or matrices would therefore comply with Article 3 of Directive 93/42/EEC and not require a CE mark.

3. 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.

Pfizer Comments

We support the possibility of hospital exemption as an important opportunity for patients to receive treatment but agree with the consultation paper that significant application may lead to attempts to avoid an application for a marketing authorisation. This mechanism should only be used in exceptional circumstances. Individual health authorities should apply the hospital exemption with substantial rigor, ensuring treatments provided under the hospital exemption meet equivalent standards as those expected for a marketing authorisation. We would also encourage consistent application between member states on application of the hospital exemption to ensure regional harmonisation.

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.

Pfizer Comments

Pfizer recognises that a great deal of the activity in the development of ATMPs is currently undertaken by research institutes and SMEs. We therefore support any measures that

encourage the development of ATMPs by these sections of industry although we believe these should also be extended to non-profit organisations.

However, we understand there have been limited interactions between the Committee for Advanced Therapies and innovators and only two applications under Article 18 of Regulation 1394/2007. Perhaps initiatives such as adaptive licensing will lead to innovators seeking more interaction with regulatory authorities.

Although the financial incentives in the Regulation are to be welcomed, we would like to see the opportunity for certification of quality and non-clinical data under Article 18 of Regulation 1394/2007 extended to all potential applicants.

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.

Pfizer Comments

Pfizer recognises the significant technological input into advanced therapies at the very early stages of product development. This work is generally conducted by research organisations or SMEs, who then generally seek collaboration with other companies to support clinical studies with their products. However, we believe Regulation 1394/2007 places most of the regulatory burden at the very end of the development process on the applicant for marketing authorisation. We believe there is opportunity for a more appropriate balance that would also encourage earlier interaction with regulatory authorities.

We would recommend introduction of a system for certification of the active ingredient of ATMPs, perhaps through an extension of the provisions of Article 18 of Regulation 1394/2007. Such a system may be analogous to the mechanisms already available for drug master files, plasma master files, vaccine antigen master files or perhaps the European Pharmacopoeia certificate of suitability. Such systems may allow for regulatory endorsement of products earlier in the development process before the initiation of clinical studies.