EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, EMA
Head of Unit

Brussels,
SANCO/D5/RSR/iv(2013)ddg1.d5.

REGULATION (EC) No. 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS

SUMMARY OF THE RESPONSES TO THE PUBLIC CONSULTATION

1. GENERAL REMARKS

The Commission should prepare a report on the application of Regulation (EC) No 1394/2007 on advanced therapy medicinal products (hereafter "ATMP Regulation").[1]

With a view to prepare this report, the Commission services launched a public consultation on 20 December 2012. Stakeholders were invited to provide their views on the requirements to obtain a marketing authorisation for an ATMP (including for combined ATMPs), on the application of the so-called hospital exemption,[2] on the incentives provided for in the ATMP Regulation, as well as on the scope thereof and its adaptation to technical progress.

This document presents a factual summary of the responses to the public consultation. It does not represent the views of the European Commission.

2. CONTRIBUTORS TO THE PUBLIC CONSULTATION

The number of contributions received was 63. It is noted that a number of entities have submitted two distinct contributions. In contrast, some single submissions have been submitted on behalf of more than one entity and, in some cases, the same contribution has been submitted by more than one entity. For the purposes of this summary each contribution submitted has been counted a single unit (with the exception of identical contributions submitted by same entity more than once).

Four contributors claimed confidentiality over their submissions. Their contributions are therefore not disclosed.

In order to facilitate a better analysis of the responses, contributors were classified in the following categories:

Sector	**Contributors included**
Academia	university hospitals and other entities involved in the research of innovative treatments
Health care sector	hospitals (other than university hospitals), blood, tissue and cells establishments
Industry	individual entities and associations of companies engaged in the development of ATMPs, medicines, or medical devices
Non-for-profit organisations	patient associations and other non-for-profit associations
Public authorities	national medicines agencies and other public authorities

[1] See Article 25 of *Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004,* OJ L 324, 10.12.2007, p. 121.

[2] See Article 3(7) of Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, OJ L311, 28.11.2001, p. 67.

An overview of the contributions by sector as well as geographical origin is provided in Annex I.

3. OUTCOME OF THE PUBLIC CONSULTATION

The ATMP Regulation was considered an important tool to improve the regulatory framework for advanced therapies in the EU by many contributors. The establishment of a dedicated body with expertise to assess this type of products and the introduction of a common framework for the marketing of these products in the EU were generally considered a positive step.

Almost a quarter of contributors had, however, a negative perception of the Regulation. The high requirements of the Regulation were blamed for the disappearance of some innovative products from the market; additionally, it was considered that such high requirements also discouraged new developments. Furthermore, the view was expressed that the current requirements do not take into account the practical limitations faced by SMEs, which constitute the majority of the entities that are currently involved in research and development of ATMPs. In the view of some contributors, this prevents the majority of developments in this area from going beyond the "hospital exemption" or other derogations under national law, thereby creating a fragmented market in the EU.

The lack of a harmonised approach on aspects such as the classification of products or the application of the hospital exemption was generally perceived as a problem. In addition, practically all contributors considered that changes should be made to the Regulation; the extent of the changes varying however from those that requested a major overhaul to those suggesting only limited changes.

1. Marketing authorisation application requirements for advanced therapy medicinal products

A significant number of contributors considered that the requirements to authorise an ATMP were not sufficiently adapted to the special characteristics of these products. It was also suggested that the European Medicines Agency does not make use of the flexibilities provided for in the legislation.

However, there was a broad spectrum of opinions as to the extent of the changes required. The main trends being:

- request for additional flexibility/clarification in the application of the requirements set out in the legislation;
- request that the data requirements be determined according to the disease, target patient and type of product (*e.g.* autologous *vs.* allogeneic, frozen *vs.* product for immediate use);
- request for major changes in the authorisation system with the introduction of a step-wise authorisation.

The request for adaptation was particularly strong in connection with the quality requirements. Contributors from the academia, hospitals, industry and non-for profit sector considered that the quality requirements should be further adapted to the special characteristics of ATMP (*e.g.* high degree of variability of the starting materials, tailor-made products in respect of which standardisation is not possible). In particular, some contributions considered that specific GMP guidelines should be developed for ATMPs. Other examples of quality requirements where adaptation was considered necessary include:

- the requirement for a qualified person to release the final product in cases where the final product is only "produced" immediately before the implantation to the patient, or
- the requirement to apply of procedures to ensure sterilisation in cases where the ATMP is composed of living cells.

Additionally, some contributions referred to difficulties in the application of the concept of "active substance" given the high variability of living materials. Others referred to the impossibility to conduct large preclinical and clinical trials. Moreover, the requirement to submit pre-clinical data was also questioned by some on grounds that pre-clinical data is not always suitable to evaluate the safety of cell-based and gene therapy medicinal products, particularly when there is already clinical experience.

Finally, in connection with the marketing authorisation procedure, a number of contributors considered that the current procedure should be streamlined.

2. Requirements for combined advanced therapy medicinal products

Approximately a third of contributions commented on the marketing authorisation requirements for combined-ATMPs. Among those, the majority considered that, if the device component is not manufactured separately, there should be a single assessment of the combination product. The CE marking was considered an unnecessary burden that did not lead to better quality of the final product. Moreover, it was even suggested by some that requiring a CE-marked device could be counterproductive as developers would tend to use devices already on the market, even if the intended use of the device is different as used in the combined ATMP, instead of developing a specific device.

Additionally, some contributors considered that the current system of validation by notified bodies of the device part was not appropriate if the intended use of the device in the ATMP is not the same as the device manufacturer's intended use. Further clarification as to the interaction between the CAT and the notified bodies was also requested.

3. Hospital exemption

The hospital exemption was the topic in the consultation that triggered most responses and it is also the area where more conflicting views were manifested.

There was consensus in that the hospital exemption is an important tool to facilitate access of patients to new treatments for unmet medical needs. The value of the hospital exemption as a

tool for innovation and research was highlighted by the majority also. Additionally, the lack of a harmonised approach to the application of the exemption was generally perceived as a problem.

The request that concepts such as "non routine preparation" or "custom-made" be explained in the legislation was common to many contributions across all sectors, with the exception of the competent authorities where the request for greater harmonisation was more nuanced. Likewise, many considered that the legislation should clearly define the quality requirements that must be respected when operating under the hospital exemption and the role of data obtained through the hospital exemption in the context of an application for a marketing authorisation.

Nevertheless, the views as to how to harmonise the application of the hospital exemption varied greatly across sectors and also within the same sector, as it is illustrated below.

3.1 Scope of the hospital exemption

Most of the contributions from industry considered that the current scope is too broadly interpreted and discourages research in ATMP by pharma companies, thereby hindering the development of new products that could be used across the EU. In general, there appears to be a perception in the industry sector that the hospital exemption is being used to circumvent the requirements for marketing authorisation. Thus, the most repeated suggestion from the industry sector was that the hospital exemption should not be permitted when there is an authorised product available. As per the type of conditions for which the hospital exemption should be permissible, the position of the industry sector was split: some contributors considered that it should be limited to pathologies with few patients, others considered that it should be kept broad.

However, the predominant sentiment in contributions from academia is that the hospital exemption is a critical tool for the development of new innovative therapies. Reference was made to the fact that some of the institutions that are more actively involved in the research and development of advanced therapies are not driven by commercial interests and that, in any case, the majority of projects are focused on rare conditions with no significant market value. Many contributions from the non-industry sector considered that the current scope of the hospital exemption should be maintained or be further expanded. However, some supported the restriction that the hospital exemption should not be applicable when there is an authorised medicinal product available.

3.2 Requirements to be applied when operating under the hospital exemption

The imposition of additional requirements with a view to get more information about products used on the basis of the hospital exemption across the EU was suggested by some contributions. The suggestions made include the creation of registries or the imposition of monitoring and reporting obligations. This view was particularly strong in the non-for-profit organisation sector.

The view that the hospital exemption should be subject to GMP was predominant in the industry sector. In the health care and academia sector, the views were split between those that considered that GMP should apply and those that considered that specific quality requirements should be developed.

4. Incentives for the development of advanced therapy medicinal products

There was wide-ranging support for the extension of incentives to academia and other non-for profit organisations. Across all sectors, it was felt that their access to scientific advice and the certification procedure would be useful to translate research into successful marketing authorisation applications.

Additionally, some suggested the extension of the certification scheme to cover other parts of the dossier, or the creation of a certification of a master file on the active substance.

5. Scope and adaptation to technical progress

It is difficult to identify a common view on the scope of the ATMP Regulation from the contributions received. For instance, some contributions considered that the definition of ATMP should be kept strict so as to increase the number of treatments that could be done by hospitals without having to resort to the authorisation procedure. However, the opposite view was also expressed; *i.e.* that a wide scope was necessary to permit assessment by the CAT.

A perception that was shared by a number of contributors is that concepts such as "substantial manipulation" or "homologous use" are not clear. It was considered that these criteria may be interpreted differently by different assessing authorities and that therefore the same product be classified as ATMP in some MS but not all; the non-binding nature of the assessment done by CAT being a further obstacle to a harmonised interpretation. Furthermore, some contributors expressed the view that tissue engineering is always a combined ATMP.

Other contributors noted that the boundaries between the ATMP Regulation and other legal instruments, such as the Directive on Human Tissues and Cells,[3] or the Clinical Trials Directive[4] are not sufficiently clear. Moreover, some considered it necessary that special rules be developed for clinical trials with ATMPs.

Additionally, some other contributors requested that the legislation better reflects the differences between autologous and allogeneic products. They considered that the application of the marketing authorisation procedure to autologous products is not appropriate given that the treatment is tailor-made, that manufacturers do not own the starting material (*i.e.* the cells) and that they can only be used for an individual patient.

---

[3] Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 07.04.2004, p. 48.

[4] Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L121, 01.05.2001, p. 34.

Finally, some contributors stressed the need to ensure rapid adaptation of the law to the fast evolution of science. Illustrations of cases where clarification of the regulatory framework was considered necessary include:

- autologous cell therapy treatments that are manufactured within a closed system that allows collection and reinjection of the cells into the donor within the same procedure;
- bioactive (growth factor loaded) medical devices,
- highly personalised products (*e.g.* product manufactured according to the specific genetic profile of a patient's tumor).

ANNEX

OVERVIEW OF CONTRIBUTIONS BY SECTOR AND GEOGRAPHICAL ORIGIN