SUMMARY OF THE RESPONSES TO THE TARGETED STAKEHOLDER CONSULTATION ON THE DEVELOPMENT OF GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 5 OF REGULATION 1394/2007

1. GENERAL REMARKS

Article 5 of Regulation (EC) No 1394/2007 on advanced therapy medicinal products (hereafter "ATMP Regulation")[1] requires the European Commission to draw up Guidelines on good manufacturing practices specific for advanced therapy medicinal products (hereafter, "ATMPs").

With a view to prepare these Guidelines, the Commission services launched a targeted stakeholder consultation on 23 July 2015. Stakeholders involved in the development, manufacture and/or commercialisation of advanced therapy medicinal products were invited to provide their views on the GMP requirements that should apply for ATMPs (including ATMPs used in clinical trials ("ATIMPs").

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 from stakeholders received was 48. While in a few cases it is unclear whether the contributions received emanate from individuals/entities involved in the development, manufacturing or commercialisation of ATMPs, all stakeholder contributions are made public for transparency reasons.

It is noted that a number of entities have submitted two or more distinct contributions. In contrast, some single submissions have been submitted on behalf of several entities and, in some cases, the same contribution has been submitted by more than one entity.

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

Sector	**Contributors included**
Academia	University hospitals and individuals/entities involved in the research of ATMPs not falling under the category of Industry, SMEs or Others.
Industry	Individual companies and associations engaged in the development and/or marketing of ATMPs, other than SMEs.
SMEs	Individual companies and associations representing companies engaged in the development and/or marketing of ATMPs that meet the EU definition of SME.
Others	Consultants, manufacturing centres, public/private partnerships/initiatives active in the area of ATMPs, *etc.*

[1] *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.

3. OUTCOME OF THE PUBLIC CONSULTATION

The approach described in the Consultation Document was supported by the majority of the respondents. The adaptations of the GMP requirements presented in the Consultation Document were deemed useful and beneficial for the development of the field. Support was particularly strong among academia and SMEs, which considered that the approach in the consultation document was generally well-adapted to the specific characteristics of ATMPs. Additionally, it has been noted that some of the adaptations proposed would contribute to reducing the cost of manufacturing and that some of the flexibilities proposed for ATIMPs would be useful for the competitiveness of the EU in the global environment.

Approximately 20% of the contributors, however, had a negative perception about the development of a self-standing Guideline. These objections were more common in the industry sector and some appear to be grounded on the perception that the intention of the Guideline is to create double standards depending on whether ATMPs are manufactured by industry or academia/hospitals.

A significant number of responses also objected to the principle that the Guideline would not apply to the hospital exemption and/or requested clarification of the scope of the Guidelines and links with general GMP rules.

The items that have triggered the majority of the comments are the following:

- Risk-based approach: there was very strong support for the application of a risk-based approach, albeit the majority of respondents requested additional guidance as to the application thereof.

- Possibility to give recognition to the quality systems established under Directive 2004/23/EC[2] and/or JACIE accreditation system: responses to this question are mixed, most support being found among academia.

- Premises: The possibility to accept the use of a clean room with a background of C or D grade for early phases of clinical trials was strongly supported by academia but different views were expressed as to whether this flexibility should extend beyond early phases of clinical trials and whether gene therapy products should be also covered by this flexibility.

  Additionally, a very large number of responses from all sectors noted that the possibility to use a background of C or D grade should be extended to the manufacture of ATMPs in closed systems or when isolators are used and that flexibility for the use

[2] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 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, 7.4.2004, p. 48).

of semi-closed systems should also be considered. Many contributors were critical as to the requirements for dedicated production facilities. In this respect, it has been noted that manufacture can take a long time (even months) and that it is not economically possible to have dedicated facilities. Several proposals have been made in this regard.

- Starting and raw materials: The adapted requirements for raw materials were widely supported among respondents from all sectors. Furthermore, the principle that ATMP manufacturers should not be required to audit blood and tissue establishments authorised and supervised in accordance with Directive 2002/98/EC[3] and Directive 2004/23/EC was supported.

  Additional adaptations have been suggested, for example, regarding the use of raw materials that are covered by a marketing authorisation (*e.g.* cytokines). Regarding the sterilisation of starting materials, many respondents considered that the preference for heat over other sterilisation methods should be reconsidered.

- Production: While most of the requirements suggested in the Consultation Document have been considered well-adapted, a number of additional modifications have been suggested. For instance, objection has been expressed to the principle that concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable, as well as to the principle of cleaning validation between the manufacturing of different batches for cell-based products. These objections have been expressed by respondents from all sectors. Additional guidance has been requested on the possibility of re-processing in exceptional cases, where the treatment of patients requires the re-administration of autologous materials.

- Qualification and validation: it was widely agreed by respondents from all sectors that a pragmatic approach is required to process validation. Various suggestions have been made.

- Qualified Person ("QP"): The adapted approach on QP oversight and release regarding products coming from third countries has been widely considered useful. Several respondents also requested that the Guideline should require that the professional qualifications/experience of the QP should be specifically adapted to the characteristics of ATMPs.

- Quality Control ("QC"): The adapted approach on sampling and testing was supported by the majority of respondents across all sectors. However, additional flexibilities and more level of detail have been demanded and several suggestions have been made in this regard.

[3] Directive 2002/98 of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

Several respondents noted that, in small organisations (particularly in hospitals), teams are multi-skilled and trained in both QC and production activities. While recognizing the importance of securing the independency of the QC activities from the production activities, alternative formulations to the text in the consultation document have been proposed to accommodate the constraints of small organisations.

- Reconstitution: The approach suggested in the consultation document was widely supported across all sectors. From the responses received, it can be inferred that there is a high degree of consensus among stakeholders as to certain activities that should be considered reconstitution.

- Automated production of ATMPs: In response to Question 25, many suggestions have been made as to how the GMP obligations should be adapted to the manufacture of ATMPs through automated devices/systems.

The above summary of comments is not exhaustive. The Commission services will carefully analyse all of the responses submitted in consultation with experts in the European Medicines Agency and the Member States.