Comments on Public Consultation Document:

Good Manufacturing Practice (GMP) for Advanced Therapy Medicinal Products (ATMP)

The comments hereby submitted intend to reflect the opinion of the 2 European Scientific associations:

- European Association of Tissue Banks (EATB);

- European Eye Bank Association (EEBA);

Therefore represent a significant part of stakeholders which activities are linked with the development of ATMPs with substances of human origin (SoHO).

Regarding the content of the document proposed for open consultation is considered:

a. Although the Article 5 of Regulation 1394/2007 requires the Commission to draw up GMP specific to ATMP, the development of specific GMP **should be preceded by a clear identification of the factors that limit the implementation of such regulations to ATMP's activities**.

   Despite the stakeholders' recognition that further adjustments may be needed, the proposed *consultation document* does not provide evidences that an appropriate evaluation was performed.

   The specific characteristics of ATMPs are well recognized and understood by the stakeholders. However, we consider that there is no justification to develop different standards applied to **products that should comply with the same level of quality and safety as the other medical products, once they are all destined to human application**. Instead, an **adaptation of particular GMP requirements should be considered** in order to answer to limitations felt by ATMP producers when dealing with SoHO.

b. By reading the proposed document, the objectives and consequences of defining "new GMPs" are not clear.

It is thought that modifications in GMP regulation must include **a prior identification of stakeholders' needs and problems, a definition of practical objectives and recognition of potential consequences of implementation of new regulation**, this way allowing the development of regulation that solve practical issues, and answers the needs of stakeholders and Competent Authorities.

In the absence of such evidences, is not understandable why it is proposed to establish different standards applied to ATMPs.

c. If ATMPs are all meant to be used in humans, different levels of GMP such "commercial ATMPs" and "investigational ATMPs" should not be considered, once the same level of safety and quality must be applied.

   In the same way, it is not clear why Hospital Exemptions (HE) is excluded.

   HE was created to provide patients the possibility to benefit from a custom-made, innovative individual treatment in the absence of valid therapeutic alternatives, under the <u>strict condition that Community rules related to quality and safety are not undermined</u>. Being so, why is HE now excluded from complying with the same requirements?

As general overview of the proposed document:

d. GMP should be unequivocally recognized as standards, easy and universally interpreted by National Competent Authorities (NCA) and stakeholders. Nevertheless, the whole *consultation document* **is very vague, and cannot be seen as guidance** for the activities developed by ATMP manufactures.

   The absence of a clear definition of requirements, can potentially lead to different interpretations by ATMP producers, with severe consequences for patients that require such therapies.

e. A **downgrade of GMP requirements is implied**, still any justification for that is clearly stated.

f. There is a general lack critical definitions (e.g. glossary), and basic GMP requirements such validation and qualification are far too simplified, and do not provide proper guidance to assure that products are safe and efficient.

This simplification in GMP requirements directly **collide with the investments already done by the ATMPs developers working in an academic or non-for-profit, that have closely worked with NCA investing and adapting their activities according GMPs**.

g. In a similar way, exclusions are done (HE and "research") without an explanation that helps to understand why some activities should not comply with GMP;

Based in all above, and without prejudice of additional further comments to the particular content of the *public consultation document*, we consider that:

1. The proposed text does not solve the technical problems associated with ATMP's specific requirements that should be adapted from GMP.

2. The future drafting of GMP Guidelines specific to ATMP by **the European Commission, should not consider the content of the current *consultation document***.

   Instead, the elaboration of future regulation must take into consideration the inputs given by:

   - Stakeholders represented by European Scientific associations (Stakeholders from tissue establishments and blood establishments/blood services);

   - Competent Authorities for ATMPs, Tissue and Blood Establishments;

   - European Medicines Agency (namely Good Manufacturing and Distribution Practices Inspectors Working Group (GMDP IWG) and the Committee for Advanced Therapies (CAT)).

Other Comments to the Public Consultation Document:

(Note that considering the incoherent structure and vague content of the consultation document, the comments hereby do not intend to do an exhaustive analysis, but highlight inconsistencies)

- (3. Personnel - Lines 152-154) Role and the training profile of the Qualified Person are critical but not addressed.

- (Q6 – Line 157) Why are we distinguishing and consider "additional flexibilities" applied to ATMPs manufactured for commercial purposes?

- (4.1. General Principles – Line 160) Besides cross contamination, there are other risks that should be considered when designing facilities: personnel circuits, products flow, level of particles, etc.

- (4.2.2. Aseptic environment - Lines 226 – 229) Why not refer to Annex 1 of the EU GMP where such requirements are properly defined?

- (4.2.2. Aseptic environment - Line 232) The terminology used in ISO 14464-1 is not grade A and grade B.

- (Q8 - Line 233) As previously mentioned: products should comply with the same level of quality and safety once they are all destined to human application. The classification of cleanrooms should be determined based on risk assessment.

- (5. Equipment Line 428) The 5 year period does not collide with the 30 years requirement defined in the Directives?

- (10. Qualification and Validation) All validation and qualification processes are very poorly defined.

- (10. Qualification and Validation – Lines 715-716) Media fill validation is really considered to add any quality warranty?

- (13. Outsourced Activities – Lines 1008 – 1034) Which is the ATMP's specificity that does not allow the reference to EU GMP chapter 7 where this requirements are correctly defined?

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