Consultation on the draft Guidelines on Good Clinical Practice (GCP) for Advanced Therapy Medicinal Products (ATMP)

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These comments are submitted by Rita Piteira (rpiteira@bst.cat) on behalf of the *Common representation of substances of human origin's (SoHO) Associations within Official Institutions of European Union* (hereafter CoRe SoHO; ID in the Transparency Register is: 501652723968-72).

This consortium brings together 4 scientific associations:

- European Association of Tissue Banks (EATB);
- European Society for Blood and Marrow Transplantation (EBMT);
- European Eye Bank Association (EEBA);
- European Blood Alliance (EBA).

CoRe SoHO is committed to ensuring that SoHO's activities in EU member states are governed by common principles of:

- Not-for-profit/non-financial gain;
- Voluntary and altruistic donation;
- Sufficiency and
- Sustainable pricing facilitating patient access to current and future therapies.

In the present submission CoRe SoHO gathers the inputs provided by members of the scientific associations.

Generic comments:
• Clearly compliance with GCP is an essential starting point for all medicinal products, but ATMPs are dissimilar to standard pharmaceuticals in many important respects (inter alia): complex and sometimes heterogeneous modes of action, difficulties in interpreting the relevance of nonclinical animal models, inherent variability of starting materials (e.g. human and animal origin), challenges in manufacturing and quality control, delivery of labile products into the healthcare environment, the need for immunological matching of allogeneic products, disentangling the efficacy and safety of the product from those of associated clinical interventions or the post-administration care of the patient and, of course, the requirement for long term traceability and follow up. • Globally this document effectively contributes to improve not only the quality of clinical research with ATMPs but also the safety of patients. • Clear and unambiguous guidelines are considered necessary tools to promote the comprehension GCPs and to facilitate their application in the context of clinical application of ATMP. • Very important aspects have been well addressed in the proposed draft document including: - the GMP concordance;

- the need for specific instructions and training for clinicians, (e.g. on reconstitution and handling before the clinical application);
- It addresses long-term follow-up including via registry or Non-Interventional Study (NIS);the traceability.

- The scope of the Guideline is limited to clinical trials but much of the contents are considered to be equally relevant whenever therapies become standard of care.
- The Guideline contains somewhat ambiguous terminology that lead to a lack of clarity. For instance, words like "sufficient" or "sufficiently" (lines 178, 335), "detailed" (lines 178, 180, 241, 243, 247, 268), "adequate" (lines 135, 262, 263, 273, 276, 295, 351) are not defined and could lead to different interpretations. Any further definition of requirements would be very welcome.
- There is no section on data management, document conservation (how and for how long?) and on people/institutions that have access to the data.
- It would be useful to explain how the label and the data sheet of the study product should be made.
- Some aspects are not specific to ATMPs and are more widely applicable e.g. lines 91-94 and lines 106-110 whereby any treatment *including* ATMPs should contemplate the potential consequences for future transplants. Consideration should be given to separating the two ambits in the document.

Specific comments (related with SoHO):

- Considers the particular nature of Substances of Human Origin (SoHO) namely in what concerns:
  - Compliance EU Directives on tissues and cells requirements for all the activities associated with donation and procurement of starting materials;
  - Includes traceability (from donor to subject and subject to donor)
  - Recognises the intrinsic variability of the starting materials and the potential associated limitations
  - Takes an overall risk-based approach - mitigating measures should be proportional to the risk
  - Several elements are in line with other relevan Guidance related with SoHO (e. g. FACT-JACIE International Standards for Hematopoietic Cellular Therapy in terms of consent and traceability for instance)
- Actions to take in case of adverse events should always be identified and clearly indicated in the protocol, and could be harmonized to cover the specific aspects of Biovigilance (monitoring and reporting) and SoHO Competent Authorities responsibilities (where applicable)
- The need for coordination between pharm and Biovigilance is even more critical considering that in the future, donors of starting materials can be simultaneously donors of other tissues, cells, organs or blood.
- We consider that SoHO used as "starting material" (building blocks / vehicle) must not be included in a patent of an ATMP since this can have potential negative effects on the availability of tissue and cells usually used as "replacement" (i.e. perhaps it can be defined as good practice that SoHO may only be used to produce experimental ATMPs if there is no waiting list for the previously established use (transplant and transfusion).)

Suggestions for improvement:
• General principles (section 1.2): it would be important to clarify which products are referred to as ATMPs in accordance with Article 2 of Regulation No.1394/2007. • Clinical Trial Design (section 2): it would be useful to identify the personnel involved and the roles/responsibilities assigned to them (for example the head of pharmacovigilance, etc.). • Clinical Trial Design (section 2(i)) (Line 95-105): specifies the need for additional safeguards in cases of paediatric population or foetuses (in utero treatment). A precise definition of those additional safeguards and their scope is needed in addition to the aspects that differentiate this guidance from the already present ICH E11 guidelines. • Clinical Trial Design (section 2(i)): in the examples shown, the categories of people "most at risk" (elderly, pregnant women, people with disabilities) are not taken into consideration. It might be useful to explain what to do in these cases and whether to include them in the study population only after the collection of data from the "average" adult population. • Clinical Trial Design (section 2(iv) (Line 118-122): Proposed change: It might be added: "When the control group patients have been exposed to invasive procedures for collection/extraction of their cells/tissues, and once the placebo-controlled trial has finished, they should be offered the ATMP treatment, provided there is evidence supporting the safety and efficacy of the treatment." • Clinical Trial Design (section 2(vii)): whenever possible a statistical analysis should be implemented in order to understand the minimum number of subjects/patients needed (considering the dropout percentage) or if a pilot study is necessary before initiating the trial (when dealing with ATMPs it is not always possible to have high numbers of subjects. If the number needed is too high because the disease is a rare disease or the follow up period is very long then alternative solutions must be proposed.). • An important phase of any Clinical Trial Design is the identification of the inclusion and exclusion criteria and the identification of the duration of the recruitment period. This should be pointed out. • Application dossier (section 3(ix)): little information is given about the Medical Devices (MD). Should the class of the MD be specified? Should any information about the presence/absence of the CE mark, Eudramed code etc. be given? Are MD-ATMP compatibility studies necessary/advisable to minimize risk? These points should be clarified. • Lines 288-90: in case of temperature deviations, no guidelines are given about what to do. Is some tolerability margin acceptable? Does the ATMP need to be discarded? Should a case-by-case be evaluated? • Informed consent (section 8.1): the informed consent should always be accompanied by an informative letter for the patient's personal physician. This should be pointed out. Furthermore, indications about the insurance coverage should always be indicated unambiguously. • Line 162-164 (+ line 401-413): The high variability of product specification in the case of ATMPs especially in the autologous settings could affect the outcome of the trial. We encourage the clarification of specific situations, for example, specifying a range of product specification (Cell dose, transduction efficiency etc…) at which the patient should be included in the final analysis. Another option could be categorizing patient population into subpopulations according to the product

specifications received. Products that did not fall into any of the specifications could be administered when the benefits of administration outweigh the risks in cases of autologous use or allogenic matched donors.

- Line 167-172: Proposed change: It might be added: "This is irrespective of the fact that information related to the risks associated to the process of taking biopsies/extracting cells as well as the potential impact on the quality and safety of the product should be included in the inform consent."
- Line 173-177: Due to the administration difficulties of ATMPs, ensuring a standardized administration process is a necessity and it can influence the final outcome of the trials as well as the safety of the study participants. Information about the training received by investigators should be duly described in the product dossier when specific or novel administration procedure is introduced, especially in the case of multi-center trials, where the activities could not be closely monitored.
- Line 193-197: Concerning the in utero gene therapy, a special consideration should be made to the mother in case of long-term follow up.
- Line 304-310: The impression received from the paragraph indicates that the presence of a sponsor or a representative during the administration of the product is not advised. However, the administration of ATMPs is a complicated process that may require the presence of supervision. We suggest that the language be more welcoming for such supervision.
- Line 312-333: We suggest including the possibility of tracing any cellular or tissue products that came in contact with the product during the manufacturing process (production of viral vectors, generation of feeder cells, etc…).
- Line 362-372: The implementation of a registry system should be mandatory for ATMPs. Due to the small sized studies usually conducted using ATMPs and the targeting of orphan diseases; the collection of real world evidence is becoming more significant. The availability of such registries will also allow the secondary use of clinical data by the EMA and researchers, which will give the scientific community as well as regulator a better understanding of the long-term safety and efficacy of these products.
- Line 374-383: More elaboration is needed regarding the remote follow-up system, particularly with the long-term follow up demanded by the EMA for ATMPs, which could extend for very long periods of time up to 15 year.
- Lines 414 – 431: Events related with the quality and safety of the Tissues and Cells used as starting materials should also be considered/highlighted as significant safety issue.