EBE Comments on

PUBLIC CONSULTATION PAPER ON THE REGULATION ON ADVANCED THERAPY MEDICINAL

The paper identifies 5 consultation topics.

1. **Marketing authorisation application requirements for advanced therapy medicinal products**
   - According to Directive 2009/120/EC, Annex Part IV, Module 3- Specific requirements regarding module 3, information on reference materials (section 3.3.2.6: A reference standard, relevant and specific for the active substance and/or finished product, shall be documented and characterised) shall be provided in the MAA. However, it should be recognised that for many ATMPs, especially autologous somatic cell therapy medicinal products, this is very challenging, and may not be possible. Could the European Commission provide additional guidance on reference materials for ATMPs.

   - According to Directive 2009/120/EC, Annex Part IV, Module 3- Specific requirements regarding module 3, relevant information on the potency (section 3.3.2.3, characterisation and control strategy) shall be provided in the MAA. The development and validation of relevant potency assay/assays is challenging. Further guidance on potency testing for ATMPs would be appreciated. Reference is made to the FDA Guidance for Industry "Potency tests for cellular and gene therapy products".

   - Annex II of Commission Regulation (EC) No 1085/2003, Section 1 (iii) states that "*modification of the vector used to produce the antigen/source material, <u>including a new master cell bank from a different source</u> where the efficacy/safety characteristics are not significantly different*" is a situation requiring an extension application, as referred to in Article 2 of the regulation. Clearly, however, this requirement is designed for continuous cell lines; in particular cell lines used for the manufacture of products of recombinant DNA technology or controlled gene expression. The situation pertaining to cell banks for manufacture of a primary cell-derived somatic cell therapy medicinal product is fundamentally different. For this reason an extension application would not be practicable in such cases for the introduction of 'new' cell banks derived from new donors. It would be appreciated if the Commission could provide additional guidance on the procedure to approve "new" cell banks.

   - The manufacturing process of many somatic cell therapy medicinal products is continuous (i.e., without a hold-step) from cell bank expansion through to the fill and finish of the cells in the primary container and storage, and can be considered a manufacturing process for the "drug product". Therefore, designation of a drug substance may not be appropriate. However, according to Annex I to directive 2001/83/EC, as amended (directive 2003/63/EC) and Volume 2B of the Notice to

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Applicants, appropriate quality information should be provided in 3.2.S and 3.2.P sections for the drug substance and drug product, respectively. A flexible approach on the information to be provided in the 3.2S and 3.2P sections of an MAA, and IMPD as well should be taken. Could the Commission develop additional guidance as to the information to be provided in the respective Module 3 sections 3.2.S and 3.2.P of the CTD for a "continuous" manufacturing process.

- Referring to Article 15 of the regulation on Traceability, could the Commission provide some insights regarding plans to draw up detailed guidelines relating to the application of paragraphs 1 to 6 of this article.

2. Requirements for combined advanced therapy medicinal products

- Article 9, section 3. of the regulation and the Procedural advice on the evaluation of combined ATMPs and the consultation of NBs (EMA/354785/201) states: "The application of a marketing authorisation for a combined advanced therapy medicinal product shall include, ***where available***, the results of the assessment by a notified body (NB)...". "If the application does not include the results of the NB assessment, the Agency....., ***unless*** the CAT advised by its experts for medical devices decides that involvement of a NB is not required".
  - It would be helpful if the Commission could give some clarification on <u>how</u> they would decide if the involvement of a NB would be required.
  - Is the Commission planning to provide further guidance on the specific content and format of the data to be submitted in Module 3, section 3.2.R of the CTD.

- Would there be a possibility of companies having <u>early advice</u> combining ATMPs (i.e. drug aspects) and devices (through device experts from a designated NB) and could this be incorporated into the pan-EU scientific advice process i.e. NBs present along with the SAWP.

- Could the Commission request the CAT to provide more transparency on:
  - the activities of the CAT combined ATMP working group
  - the EMA-CAT-NB interactions and updated work plan.
  - It would be helpful if industry, academia, and other organisations could have the opportunity to play a role in facilitating these efforts, e.g., through Eucomed, EBE, etc.

3. Hospital exemption

- The research industry would agree with the statement in the Consultation Paper that "...too large application of this exemption may discourage the application of marketing authorisations."
- A clearer description of the hospital exemption is required. The requirements for HE products at national level are not clear (i.e. what is exactly meant by "non-routine basis"; "preparation according to specific quality standards"; "individual patient" [can be mixed

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with autologous product]) and are not harmonised across the EU. Help from the Commission to encourage member states to establish clear guidance would be welcome.

- See EBE paper on Hospital Exemption and joint industry letter of 17 December 2012.

4. Incentives

- Please consider incentives with regard to speed or frequency of meetings.

- Please consider incentives for orphan ATMPs and ATMPs developed for rare indications regarding openness to accept novel approaches to trial designs and patient populations beyond what is addressed in the "Guideline on clinical trials in small populations (CHMP/EWP/83561/2005)". For example, it may be that placebo arms are not required or the length of follow up of the trial can be a novel approach as opposed to traditional clinical development.

- Could the Commission consider providing (or consider granting) accelerated assessment according to "Guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004 (EMEA/419127/05)" in cases where this has occurred.

- The Certification Procedure is limited to use by SMEs. In order to encourage the development of orphan medicines, would it be possible to extend this procedure to include other companies involved in OMP development.

5. **Scope: Elements that could be considered to ensure that the scope of the Regulation takes account of technical progress include**

- "On work with HTAs, the COMP noted: "The agency is working with EUnetHTA [an organization that focuses on scientific co-operation in HTA in Europe] towards a better understanding on orphan designation, marketing authorisation of orphan medicines and national competent authorities' initiatives on availability of designated orphan medicines. The dialogue takes the specific characteristics of orphan medicines and the rare conditions they are used for into consideration, and will explore ways of sharing information for the common benefit of patients affected by rare diseases and the financial sustainability of the healthcare systems." * Can the Commission do the same in consideration of the particular characteristics of ATMPs.

6. Additional comments

- An important general comment on the current registration procedure concerns the collaboration between the CAT and the CHMP. In order to provide regulatory predictability and timely decisions, it would be helpful if the working procedures of both groups could be clarified and the cooperation strengthened.

- Currently, the "Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials" (EMA/CHMP/BWP/ 534898/

2008), is the leading guidance for the preparation of an IMPD of an ATMP. Some of the requirements described in this guidance may not be fully applicable to specific ATMPs. Would the Commission consider drafting additional guidance for ATMP IMPDs.

- It would be highly appreciated if the Commission could develop additional guidance for tissue engineered products, beyond the reflection paper on clinical aspects specific to tissue engineered products (EMA/CAT/CPWP/573420/2009), and combined advanced therapy medicinal products, e.g. focusing on quality and non-clinical aspects.

- As many sponsors develop their ATMPs globally, they would benefit from harmonization of the development requirements among the different regions, e.g. ICH guidances. Currently, global standards, e.g. for donor testing, are lacking. Does the Commission intend to encourage the EMA/CAT to work more closely with the FDA, Health Canada, the PMDA, and potential other NCAs on developing global guidances for ATMPs.

- Could the Commission provide guidance on the status of products that have undergone the CAT Certification Procedure. This would be helpful in subsequent discussions between the developer and potential collaborators or with non-EU regulatory authorities.

- When is the Commission planning to publish a general report on the application of the regulation 1394/2007/EC.

- Sponsors developing allogeneic products for rare diseases indications are frequently obliged to conduct multicounty studies. Each national Competent Authority has its own requirements regarding the viral safety for the selection of donors for allogeneic products. For allogeneic products, sponsors are fully dependent on the tissue establishment for sourcing the human raw material. When conducting a clinical trial with cell-based medicinal product, the sponsor is required to meet the requirements of each national regulatory body. This is not the role of the Tissue establishment but, to an extent, the applicant is dependent on the processing and the release performed by the Tissue establishment. The additional testing required by some national competent authority cannot always be supported by the Tissue bank with which the CT sponsor has a contact. In addition, the Tissue establishment is not always equipped to perform additional tests in GLP certified conditions. A guidance from the CAT/EMA to encourage harmonisation of the viral evaluation requirements by member states would be welcome.

*SCRIP Intelligence, 18 Feb 2013, EMA's orphan committee to boost work with international HTAs