

March 30, 2013

European Commission, DG Health and Consumers
Unit D5 'Medicinal products – authorisations
EMA

Re: Public Consultation Paper on the Regulation of Advanced Therapy Medicinal Products

Dear Sir/Madam:

The Europe Legal & Regulatory Affairs (LRA) Committee within ISCT (International Society for Cellular Therapy) has reviewed the Public Consultation Paper on the Regulation of Advanced Therapy Medicinal Products and would like to take the opportunity to provide comments on the consultation topics. We appreciate the opportunity to respond with feedback reflecting our stakeholders from both academic and industry settings. Specific comments are included below.

We thank the EU Commission for providing this forum for feedback and would be pleased to address any questions you may have.

on behalf of the ISCT EU LRA Committee,

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Public Consultation Paper on the Regulation of Advanced Therapy Medicinal Products Comments from the ISCT EU Legal & Regulatory Affairs (LRA) Committee

2.1. Marketing authorisation application requirements for advanced therapy medicinal products

1. Clarification and guidelines on the following points would be appreciated:

- The dossier is organized according to a "classical drug" and thus some chapters do not seem to fit very well with cell-based therapeutics. For example, pharmacokinetics and pharmacodynamics are very difficult to document in a dossier of cell therapy.
- Guidelines that reflect expectations regarding non-clinical and clinical data that needs to be generated to support MAA for ATMPs. Clarification would also be appreciated for specific circumstances in which it might be difficult to conduct sufficiently powered, randomized controlled trials, for example when the cell-based product is an orphan drug (and has orphan-drug designation).
- Guidelines on the characterization of cell-based medicinal products.
- Tumorigenicity
General Comment: Guidelines for tumorigenicity are available for biologics and drugs however they do not always or not completely apply to ATMPs.
 - We request for clarification and specific guidelines regarding when tumorigenicity studies are needed for ATMPs
 - When required, we request for clarification on acceptable alternatives if suitable animal models are not available.
- 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, putting down a product specific reference standard/reference material is for many ATMPs, especially autologous somatic cell therapy medicinal products, very challenging, if possible at all. Establishing reference materials in primary human cells seems particularly difficult since it also involves several precise steps in cell processing including standards for phenotype, function, differentiation, proliferation and others. These steps should also consider tissue sources taking into account many different ex-vivo culture conditions. Could the EU 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, characterization 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".
- Referring to Article 15 of the regulation on Traceability, could the EU Commission provide some insights as to when the detailed guidelines relating to paragraphs 1 to 6 will be available?

2. Annex II of Commission Regulation (EC) No 1085/2003, Section 1 (iii) defines that *"modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not*

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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 and 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 which 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 EU Commission could provide additional guidance on the procedure to approve "new" cell banks.

3. 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 & 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 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 as to which information to be provided in the 3.2S and 3.2P sections of an MAA, and IMPD as well, should be taken. Could the EU 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?

2.2. 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 EU Commission could instruct the CAT to provide clarification on how they would decide if the involvement of a NB would be required.
 - It would be helpful if the EU Commission or the CAT can 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 early advice combining ATMPs (i.e. drug aspects) and devices (through device experts from a designated NB) and whether that could be incorporated into the pan-EU scientific advice process i.e. NBs present along with the SAWP or whether it would be a unique separate procedure?
 - Could the EU Commission instruct the CAT to provide more transparency on:
 - the activities of the CAT combined ATMP working group
 - the EMA-CAT-NB interactions and work plan
 - It would be helpful if industry, academia, and other organisations could get the opportunity to play a role in facilitating these efforts, e.g., through Eucomed, EBE, etc.

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2.3. Hospital exemption

This is a hotly debated topic which is due to interpretation difficulties of the current regulations as reflected by the inconsistent implementation of HE in the Member States. Furthermore, interest differences regarding the hospital exemption (HE) exist between industry and academia. In general, the requirements for HE products at national level are currently not sufficiently clear (i.e. what is meant by “non-routine basis”; “preparation according to specific quality standards”).

Industry is concerned that there is a risk that the HE is applied incorrectly allowing for a parallel circuit for small-scale, locally produced ATMPs competing with centrally authorised products. Thus, as a general policy, hospital exemptions should no longer be allowed in those situations where a fully validated, centrally approved ATMP is available for the same indication in the same patient population which is fully supported also by our academic members. We therefore suggest including this provision in the regulation.

On the other hand, academic stakeholders are concerned that availability is secured for ATMPs that have been part of established clinical practice prior to the introduction of the regulation on ATMP and also for coming products with proven clinical efficacy but lacking marketing authorization. For these products, for which centrally authorized alternatives are not available, the current HE is too restrictive and ATMP regulations need to be amended accordingly.

ISCT requests advice from the EU Commission regarding how to deal with the situation where an ATMP does not have marketing authorization but efficacy has been proven.

ISCT would request the EU Commission/CAT/EMA for a dedicated session with interested parties' representatives for discussion of this topic ahead of any further guidance or legislation.

2.4. Incentives for the development of advanced therapy medicinal products

- Fee reductions and waivers for EMA activities are valued in an industry that is poorly funded and dominated by SMEs. ISCT encourages the Commission to continue to support these incentives until the field matures.
- ISCT recommends that the Commission considers qualifying not-for-profit (non-commercial) members for these incentives (specifically scientific advice and the certification procedure). Since academic institutions are one of the most important carriers of scientific development and progress, they should have a well-defined place within the incentive programme. These stakeholders rely on successfully partnering or licensing their technologies to companies for commercialization. Currently, industry is looking for at least phase II data; therefore it is critical that these non-commercial members have sufficient access to scientific advice to lay the ground work for commercial requirements.
- Similarly with topic 2.3, ISCT would request the EU Commission/CAT/EMA for a dedicated session with interested parties' representatives for discussion of topic 2.4 ahead of any further guidance or legislation.

2.5. Scope and adaptation to technical progress

No comments

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Additional Comments

- 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 or not fully be applicable to specific ATMPs. Will the EU Commission consider drafting additional guidance for ATMP IMPDs?
- It would be highly appreciated if the EU Commission could develop additional guidance for tissue engineered products and combined advanced therapy medicinal products.
- 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 EU Commission intend to work more closely with the FDA, Health Canada, the PMDA, and potential other NCAs on developing global guidances for ATMPs?
- Greater clarification on how to assess equipment (i.e. CE marking) used in the manufacturing of ATMPs would be appreciated.
- ATMP reimbursement: there is a large lack of definition on what a specific product would be reimbursed. This will certainly be of help for both academic and corporate developments on ATMP.