International Society for Cellular Therapy
ISCT
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Comments from the ISCT Europe Legal & Regulatory Affairs (LRA) Committee

ISCT Comments on European Commission Consultation Document ‘Good Manufacturing Practice for Advanced Therapy Medicinal Products’

General comments
1. We appreciate the effort the Commission has undertaken to address GMP aspects, unique to ATMPs and are pleased to be asked to provide input. Our comments have been subdivided into general comments and answers to the questions.
2. As GMP is not a standalone set of requirements, it is suggested to refer to appropriate GxP (GCP, GDP) guidances.
3. ISCT members propose to change the statement of lines 73-74 as follows: “Manufacturing of ATMPs under the hospital exemption is not within the field of application of this consultation document since it is under the responsibility of each Member State National Competent Authorities to regulate and define standards for this activity. Meanwhile, article 28 of Regulation 1394 requires for HE ATMPs quality standards equivalent to ATMPs for which authorization is required to safeguard patients”.
4. The absence of cross-references and the fact that most of the text of this document is copy/paste or paraphrase from EudraLex Volume 4 suggests that the intent is to provide a standalone document which is a ‘one stop shop’ on GMP for ATMPs. Such a document would be useful. We are, however, concerned that the level of detail included in the document currently may create risk for developers who are not experienced with pharmaceutical production. - As example, 4.2.2 includes the statement that “the premises should be fully validated”, but there is nothing in this document that provides guidance on what “fully validated” means, nor is there a cross-reference to Volume 4, Annex 15, where the relevant guidance may be found. There is a need to either include or cross-reference significantly more of the text from Volume 4. If it is not the intent that this be a standalone document, then further introductory text is required to position this with existing GMP expectations. - From an overall perspective this document covers some aspects of GMP from both the Medicinal Product and IMP areas that are covered in the general GMPs and Annex 13 replacement (CTR Delegated acts on GMP for IMP). By doing so it sets up divergence of guidance and in some cases weakening of Patient Safety where it is not appropriate, even for the special circumstances of ATMPs. As a conclusion - where it is not a specific need for ATMP the guideline should refer to the main GMPs for Medicinal Product and IMPs as a principle of convergent rather than divergent regulation and guidance. If this principle is not accepted then significant sections of this ATMP document will need comparing against EudraLex - Volume 4 GMP chapters and annexes strengthening to maintain patient safety. Annex 1 being probably the most important.

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Comments on the specific questions raised
Q1: Are the principles laid down in Section 2 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
A RBA for GMPs is appropriate and allows for flexibility to meet the development and commercialization needs for ATMPs. More flexibility in early clinical development/FIM trials may be possible. This could be incorporated in this GMP document or be developed as a separate guidance on "RBA for GMPs of ATMPs" with examples.
Q2: Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline? In the affirmative, please provide examples.
Yes, we consider this as useful. Examples: 1) The RBA should be applied to justify a tailor-made GMP system for e.g., autologous ATMPs, ATMPs used for (ultra) orphan indications, allogeneic 1 donor: 1 recipient ATMPs, and manufacturing processes which do not involve open manipulation steps of the cells/tissues, or involve semi-closed manipulation steps. 2) A risk assessment on additional safety measures (e.g., in-process testing, product release testing, additional characterisation of the cell/tissue starting materials and animal and human-derived raw materials used in the manufacturing process, patient monitoring) should be considered for ATMPs lacking viral removal and/or inactivation manufacturing steps. This is of great importance due to the biological nature of raw and starting materials (see also lines 483-484). 3) Meeting the requirements of sterility as per the EP (2.6.27), i.e., sample volumes, number of retains, etc.) is not always possible for cell and tissue based products because of the limited amount of the product, short shelf-life (retains), etc. 4) The RBA should be applied where it is not possible to qualify active substance and/or DP specific reference standards and materials 5) The RBA should be used to assess the need for fail safe processes as potentially, there is no chance for rework or repetition (also refer to chapter 9 on production) 6) The developer is encouraged to write a standalone document that summarizes all (potential) risks and the measures taken to prevent them.
Q3: How should the quality systems established in accordance with Directive 2004/23[2] be recognised in terms of GMP compliance for products that are ATMPs solely because the use of the relevant cells/tissues is for a different essential function in the recipient as in the donor (i.e. the manufacturing process does not involve any substantial manipulation)? What about the JACIE accreditation system?
- As this particular category of ATMPs are regulated under directive 2001/83 EC but have the same characteristics as non-substantially manipulated transplant/transfusion products used for the same essential function in the donor and the recipient, which are regulated under

Directive 2004/23/EC, as amended, or Directive 2002/98/EC, the technical requirements for donation, procurement, manufacturing, storage, and distributions of these products are appropriately covered by JACIE standards. However, the GMP manufacturing license should remain under the responsibilities as laid down in Directive 2001/83 EC. Consequently, we agree that JACIE standards, but not the JACIE accreditation system, could be recognised in terms of GMP compliance for this category of ATMPs.
Q4: Are the requirements laid down in Section 3 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
- The requirements as laid down in section 3, Personnel, seem to be appropriate. The main areas where section 3 could be further developed is: - The concept of cross-contamination (lines 147-151) - The training and qualifications required to become a Qualified Person should be related to the specifics of ATMPs, e.g., having a basic scientific understanding of tissue and cell biology, biotechnological techniques (e.g., cell banking system, viral vector system and manufacture, including up- and downstream processing), adventitious agents safety testing, and on the job GMP training specifically related to the manufacture of ATMPs. Where the QP is responsible for the release of combined ATMPs, he/she should have a basic understanding of the device/scaffold and it's manufacture & release under QMS, as is appropriate for any QP releasing combination products.
Q5: Are the requirements laid down in Section 4 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate..
- The requirements as laid down in section 4, Premises, seem to be appropriate.
Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?
- Appropriate. No comment.
Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials
- See answer to question 2, example #1 (RBA to be taken).
Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to

withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)
Safety of the patients is of great importance throughout clinical development and once a product is commercially available. If a less stringent room classification approach is taken during early clinical development (FIM trials), this should be justified and should be based on a risk assessment (Q/S impact). For an autologous or allogeneic 1:1 (safety impact applies to one and not multiple patients) minimally manipulated product, where semi-closed systems are used for the manipulation steps and adequate in-process and product measures (testing) are in place and patients are put on a stringent safety monitoring programme, it may be acceptable to justify a less stringent (i.e., grade A with a background C/D grade) room classification. The patient population and severity of the disease should be part of the risk assessment. The following steps are recommended to establish the appropriate manufacturing environment for FIM trials: (See FDA guidance on GMP for FIM investigational ATMPs http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf) • A comprehensive and systematic evaluation of the manufacturing setting (i.e., product environment, equipment, process, personnel, materials) to identify potential hazards • Appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards to safeguard the quality of FIM ATMPs • To be acceptable also for those products undergoing conditional release before the availability of the sterility testing (microbial, mycoplasma, etc) lack of microbiological contamination must be demonstrated throughout process development, including process verification and validation, to justify a class C/D surrounding class A biosafety cabinet for the manufacturing process. • Cross contamination can be avoided by manipulating one product (if autologous one batch) at a time in a class A biosafety cabinet. Deviation from this rule needs a careful risk assessment.
Q9: Are the requirements laid down in Section 5 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- No comments
Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.
- No comments
Q11: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?
- ATMP's manufactured for commercial use would follow the same principles regarding quality systems as more traditional pharmaceuticals. For example, a Quality Management system which includes CAPA, Change Control, Documentation Control, Batch Records, Excursion and Investigation Records etc. would still apply to ATMP's. There may be some difference in application, but the principles would be the same.

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Q12: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.
- No comments
Q13: Are the requirements laid down in Section 7 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- Generally, these requirements are appropriate. - In case clinical/pharmacopoeia grade raw materials are not available for late phase clinical development or commercial production, a RBA should be applied to determine which additional (in-house) testing may be needed or if there are other alternatives available.
Q14: Are the requirements laid down in Section 8 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- No comments
Q15: Are the requirements laid down in Section 9 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- Generally the requirements are appropriate. - For FIM/early clinical development, cleaning verification, based on a RBA, rather than cleaning validation may be appropriate.
Q16: Are the general principles laid down in Section 10 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- Additional details concerning process qualification (i.e., control and process monitoring) for investigational ATMPs are suggested. A RBA should be taken to assess the process qualification requirements for each stage of development.
Q17: Due to the biological variability inherent in ATMPs and limited batch sizes, process validation is particularly challenging for ATMPs. A pragmatic approach as to the specific requirements on validation should be developed. Please provide suggestions.
- The principles of process validation can be applied using a RBA. ATMP's pose several challenges, which will require control strategies based on a risk assessment, taking the complexity of the process steps, whether or not it is an (ultra) orphan disease, and/or autologous & allogeneic (1 donor: 1 recipient) product into account. - Adaptive approaches may be possible, where there is a continuous verification of the process (IPC/PMT) and assessment of release and stability data, rather than an $n \geq 3$ validation batches (see also Annex 15). This does not preclude the qualification of individual steps.
Q18: Are the requirements laid down in Section 11 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early

stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- See the answer to question 4: the training and qualifications required to become a Qualified Person should be related to the specifics of ATMPs.
Q19: Are the requirements laid down in Section 12 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- A RBA (flexibility) is suggested with regards to reference and retention samples for autologous products and possibly also for other small batch size products (e.g., allogeneic 1 donor: 1 recipient; ultra-orphan disease FIM trial). - A RBA should be taken for the storage of starting materials with a short-shelf life. Sometimes the storage of 2 years may not be feasible and even not needed, like for investigational ATMPs. The duration of the clinical trial should be taken into account.
Q20: Are the requirements laid down in Section 13 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- This section needs extension to include additional GMP activities beyond manufacture, like pack & label, storage, and distribution.
Q21: Are the requirements laid down in Section 14 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- This section needs extension to include quality defects & complaints, adverse events reporting, etc.
Prior to administration to patients, ATMPs may require certain additional steps after they have been released by the QP of the manufacturer. These steps are generally known as "reconstitution". Examples of reconstitution include thawing, dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes). Reconstitution is typically conducted in a hospital. *Q22: Do you agree with the principle that, where reconstitution of the finished ATMP is required, the manufacturer's responsibility is limited to the validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users?*
- Yes we agree.
Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?
- Yes, we agree that reconstitution is not manufacturing and is therefore outside GMP. - It is suggested to change the word "reconstitution "to "product handling for clinical application" as it may be mixed- up with the reconstitution of a lyophilised product.
Q24: What activities should, in your view, be considered as reconstitution?
- Thawing steps, dilution steps, preparation of the administration system (e.g., surgical device, syringe). In fact all handlings which do not change

the characteristics of the active substance(s). It may not include additional cell culture steps after release of the product.
Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges. *Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?*
- Autologous therapies which would enable fully automated cell processing at a patient's bedside with cells being taken, loaded into the equipment, manipulated, and sometime later the finished product being taken for administration (point of care systems) may require additional definitions of roles and responsibilities (R&R) of the device manufacturer, medical doctor and responsible person or QP to release the product. These R&R should be defined in written contracts between the different players. - The GMP obligations need to be covered by the site of use of the automated equipment. The manufacturer should be obliged to support with all necessary information and training the responsibilities of the site of use. There is a difference between the technical functionality and capability of the automated equipment and the process and product it is used for. The former should be covered by the manufacturer of the equipment (under device legislation; QMS), the latter by the site of use (medicinal product legislation; GMP; tissue establishment responsible person or QP).