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Submission of comments on Consultation Document Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Art. 5 of Regulation 1394/2007

Dear Sir / Madam

Thank you for the opportunity to comment on the above document.

The following represents the views of the company, **Cell Medica** on the consultation document. Cell Medica develops, manufactures and markets personalized cellular immunotherapeutics for infectious disease and cancer.

Cell Medica falls within the EU definition of a small and medium sized enterprise (SME). It has a global presence with sites in the EU (London and Berlin) and the USA (Houston). Company headquarters are based in London.

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Kind Regards

Seb Hodgkin

General Comments

Cell Medica very much welcomes the fact that the EC is considering the development of specific guidance for GMP for ATMP's. It continues to be a challenge for many companies in this field to interpret and apply all aspects of GMP as currently written due to the intrinsically different nature of many ATMP's and their manufacturing process to conventional pharmaceutical products. There are many other groups of pharmaceutical products e.g blood products, radiopharmaceutical, IMP's etc that require and have specific regulatory guidance and ATMP's clearly are a category that would benefit from such guidance.

The implementation of such legislation should be performed in an unambiguous manner such that there are no conflicts or misunderstanding of expectation between any new legislation and existing GMP, otherwise this removes the benefit of this initiative.

The difference in requirement for Investigational ATMPS and Non-investigational (Marketed/Licensed) ATMP's should be made very clear and made consistently throughout the document.

There are several specific points in the guidance that implies that a requirement is more or less relevant to a particular type of product (e.g. cellular or Gene based). It is not always clear why there is this distinction.

There may be scope to highlight different approaches to production of an ATMP for an individual specific patient (individualised product) vs production of a batch of product for small to large number of individualised products. From a public health protection perspective, the risks are different.

A glossary of terms should be developed to ensure common understanding.

Comments to specific questions in the draft text

1. Introduction	
	No specific comments
2. GMPs for ATMPs: general principles	
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?).	Yes
Please provide comments on the text below as appropriate.	n/a
Q2: Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline?	General content of section 2 is satisfactory. The additional information regarding risk assessment is not deemed to be sufficiently detailed on how this can be applied to be of much benefit. There should be an emphasis that risk based principles should be applied and that some degree of risk based flexibility is acceptable. Reference to risk based approach in ICHQ10 could be made to avoid repetition.

In the affirmative, please provide examples.	n/a
Q3: How should the quality systems established in accordance with Directive 2004/23 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)?	It's not obvious why Quality system requirements should automatically be different depending on whether the cells/tissues are used for the same or different essential function in the recipient. I.e. products made using a process that doesn't involve substantial manipulation should be treated similarly regardless of whether the use in the recipient is for a same or different function, *unless* there is an identifiable reason why use for a different function increases risk and additional controls may be needed. (e.g. administration of cells into a different bodily location from normal could increase risk.). The acceptance of Quality Systems established for 2004/23 may be suitable in some cases but not in others. This may be addressed on a risk-basis.
What about the JACIE accreditation system?	Concerning the JACIE accreditation system it can be said that this system provides a very detailed set of standards that are independently audited that maintain the quality of the tissues and cells and so should be recognized as a suitable standard to help assess for safety and reproducibly processing and testing cellular products. It would be down to the manufacturer to determine if suitable based on their requirements.
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?).	Mostly yes.
Please provide comments on the text below as appropriate.	Lines 131-132 state "All personnel involved in the manufacturing or testing of an ATMP should have a clear understanding of its tasks and responsibilities." This is unclear. The word "its" seems like it would refer to the ATMP, or possible the mfr or testing, but none of those possess tasks or responsibilities. Presumably the tasks & responsibilities belong to the personnel, in which case "its" should be replaced by "their". Lines 148-151 are not well specified. E.g., passage from an area containing GMOs or "toxins" to another area should only be avoided to the extent that such passage could reasonably lead to cross contamination. As currently written, this passage doesn't differentiate between situations with very high risk of cross contamination versus ones with no such risk.
4. Premises	
Q5: Are the requirements laid down in	In general yes, however a number of areas should be

Section 4 sufficiently well-adapted to the specific characteristics of ATMPs?	clarified
Please provide comments on the text below as appropriate.	There is no reference to EU GMP Annex 1 for cleanroom limits including microbiological limits. Line 231 only refers to ISO 14644 but this does not provide details of EU Grading, which is used throughout this document. Line 232 : The information is vague as it implies early stage trials can be performed in a different environment. It is not always known upfront if a trial will be a pivotal study. Line 232/233 also uses the wording 'In general'. We agree there may be situations where this is not required and would be dependent on the product / process. Clear situations where a different environment from A / B would be acceptable should be provided. E.g. using fully closed systems, use of isolator technology or potentially products that can be filter sterilized (e.g. certain in vivo gene therapy products). As written, this seems excessive for some products and not consistent with a risk-based approach. In general, there should be some reference to the potential use of isolator technology as this is an area of interest for the manufacture of ATMP's from both an aseptic and containment perspective (e.g. genetically modified cell therapies). Line 234: a definition for large scale is required
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?	Generally, no as Grade A/B should be used for any open steps. It could be stated that some flexibility to the environment can be employed to processes where the closed systems are employed and connection etc. can be made without compromising the product or using isolator technologies. A universal definition of what is meant by an open and closed system or process would be useful.
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.	No - the maintenance of an aseptic environment is essential to the production of an injectable product which cannot be sterilised regardless of phase of development.
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	No Microbiological control testing is not sufficiently sensitive to ensure 100% the absence of microorganisms. Unclear on why Gene Therapy IMP's were excluded in the

products), provided that the specific risks are adequately controlled through the implementation of appropriate measures?	question.
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.)	This would introduce unacceptable safety risk for an injectable product. A in B is a proven standard for sterile products produced by aseptic processing. Any lower grade will result in elevated risks of contamination. For products which can't be terminally sterilized which is the case for cell products there is no "appropriate measure" available.
5. Equipment	
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)?	Yes.
Please provide comments on the text below as appropriate.	Need to consistently state the requirement to maintain records, e.g. on equipment maintenance, cleaning/sterilization, containment testing, water pipe sanitization sections don't mention keeping records, but subsequent paragraphs do.
6. Documentation	
Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs?	Yes
Please provide comments on the text below as appropriate.	page 13, line 316: The term Product Information is widely used for the documents accompanying the product upon shipment and could be misleading Page 13, line 343: Contracts with suppliers of biological raw materials are considered mandatory? Line 313. Is a site master file not currently required by all sites holding a manufacturing license, not just those involved in commercial manufacturing including IMP's? Line 337 to 339. This statement is welcome. Line 343. Unclear if statement 'contracts and quality requirements agreed with third parties applies to all raw materials or those of biological origin'. For Investigational

	ATMPs having contracts and quality agreements for all raw materials seems too stringent. Lines 417-419. The note is unclear. Line 438. Unclear why the 30 year traceability requirement only applies to cell based products
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?	No
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, however the requirement for a contract and quality agreement for each biological raw material in a less defined (early phase) process is too stringent. This should at least be risk based.
7. Starting and raw materials	
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)?	Yes, generally. Line 466 - the acceptance of licensed blood and tissue establishments without the need for additional audits is fully endorsed. Implementation of this will greatly aid the development and provision of individualised patient therapies manufactured from materials procured from licensed establishments.
Please provide comments on the text below as appropriate.	Line 452 should this read "5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS" currently in draft. Line 481-484. We are not sure why this is specific to cell-based products as it should apply to any ATMP where sterilisation is not possible.
8. Seed lot and cell bank system	
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)?	Yes
Please provide comments on the text below as appropriate.	Line 530 : It should be recognised that evidence of stability may occur concurrently for investigational ATMPS.

9. Production	
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?)?	Yes but with some clarifications
Please provide comments on the text below as appropriate.	Line 611 'preferably is a standard format throughout the facility' should be removed. There is evidence to show that having differing styles, colours and appearance of labels for similar items can reduce errors. Line 618 the sentence "Mix-ups of dedicated (autologous) materials should be prevented" should be changed to materials for individual patients or equivalent. Mix ups of all materials should be prevented but this is just as important for an allogenic product as for a specific patient. Not always autologous. Line 628 'separation in place' is somewhat vague. Allowance should be made where certain product stages require incubation of products in the same space. It may not be feasible to separate each lot of a given product, particularly for small scale individualised patient production. Some degree of risk assessment should be performed e.g. depending on whether the incubation is performed in an open or closed state. Add to the separation requirement "unless completely closed processing is applied". Line 648 cleaning validation is not appropriate to be conducted between every batch of a cell based product where individualised patient products are made using single use disposable items of equipment. In this cases verification of a change over process between different lots may be more appropriate for this type of product. Any principles should apply to all ATMP's not just cell-based ones. Line 652 we do not believe this is true if closed vessels are used for centrifugation.
10. Qualification and validation	
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?)?	Yes
Please provide comments on the text below as appropriate.	Line 724 : should be clarified to state that in line with the expectation that investigational ATMP will not be validated to the same extent as commercial ATMP's, the same applies to changes made to investigational products.

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.	We agree that a pragmatic approach must be applied. For early stage development prospective validation may only be possible using simulated starting material or that from healthy donors and this may be different from starting material used to manufacture product for clinical use. An acceptance that pre-determined acceptance criteria may not be met when validation is performed on material from patients and in the early phase specifications may need to be revised. A concurrent validation approach may be more applicable with regular reviews of data from the manufacture of clinical lots.
11. Qualified person and batch release	
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?)?	Yes
Please provide comments on the text below as appropriate.	n/a
12. Quality control	
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?)?	No, many areas should be clarified
Please provide comments on the text below as appropriate.	Line 895 : There may need to be some flexibility around the total independence of QC and production in the case of very small scale manufacturing for investigational ATMP's where individuals in teams may be multi-skilled and trained in both QC and production activities. QC activities must be performed by a trained individual independent of that specific production activity. Line 922 to 924 : Some guidance is needed for the manufacturing of individualised patient product where a single or very few units are produced. Retain and reference samples may not be possible for an individual patient product where only one or a very small number of units may be manufactured. In those cases any potential retention and reference samples cannot always be fully representative and may not be in sufficient quantity for full testing. Line 928: The retention of primary packaging and some expensive (non-biological) reagents ordered and made on demand is a huge burden and of very limited value and due to sampling constraints (often only one item is ordered)

	rarely helpful in quality defect investigations. Line 938 : It is not practical to retain samples of biological starting materials for individualised patient products. E.g. where the starting material is fresh blood. Line 957 : In the same way process may not be fully validated for investigational ATMP's the same should apply to test methods. Those concerned with safety should be at all stages. Other tests may be performed for information only and may not be validated at this stage of product development. Line 985 : states trending is not required for investigational ATMPS however we feel this should be performed at all stages to determine what is important to product quality and what may not be. This is particularly recommended during early product development. Line 1000 : There should be guidance on stability expectations for investigational ATMPS
13. Outsourced activities	
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?)?	Yes
Please provide comments on the text below as appropriate.	n/a
14. Quality defects and product recalls	
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?)?	Yes
Please provide comments on the text below as appropriate.	n/a
15. Environmental control measures for gene therapy products	
16. Reconstitution of product after batch release	
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	Yes

of reconstitution to the users?	
Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?	yes (both for ATMP and ATIMP)
Q24: What activities should, in your view, be considered as reconstitution?	Reconstitution may encompass: dissolution or dilution with solvent; thawing, transfer to infusion bag, syringe; but not buffer exchange.
17. Automated production of ATMPs	
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?	This depends on the nature of the device. If automated devices are used as significant but not total part of the manufacturing process, then the requirements are no different from any other equipment (the manufacturer must ensure the adequate design and validation of the equipment (including computersized systems and data integrity) and will need to provide data demonstrating the capabilities of the technology and the performance of the equipment. The manufacturer will be responsible for the evaluation of such data for their specific purpose and then demonstration of its suitability for the given process.). Ultimately the manufacturer (license holder) will be responsible for the product quality. The responsibility for product quality is a lot less clear for fully automated equipment that manufactures a final product (e.g. Vein to vein). In these cases the responsibility must be shared between the equipment manufacturer/supplier and the license holder. E.g. Quality attributes that can only be affected by the automated parts of the process would be primarily the responsibility of the equipment manufacturer but any variable aspects e.g. suitability for a particular patient or environmental factors would be the responsibility of the product manufacturer. The equipment would need to be developed and validated as per pharmaceutical requirements. Suitable agreements would have to be in place to clearly define these and how this relates to release by the Qualified Person. We think this is an area which may need further evaluation and evolution of GMP as more of these systems are brought to the market.