Action to Focus and Accelerate Cell-based Tolerance-inducing Therapies (A FACTT)

Barcelona 11.11.2015

Comments on Good Manufacturing Practice for Advanced Therapy Medicinal Products

Dear Sirs,

With this letter we are sending our comments on Good Manufacturing Practice for Advanced Therapy Medicinal Products, which has been published for public consultation on EMA webpage, recently. Please find attached our suggestions.

Action to Focus and Accelerate Cell-based Tolerance-inducing Therapies (A FACTT) (www.afactt.eu) is a paneuropean community funded by European Cooperation in Science and Technology (COST www.cost.eu) under the grant no BM1305. We are academics from 18 different countries/universities working on translation of tolerogenic cell-based therapies into clinical practice, which is mainly R&D activity. The attached document was consulted among our members and A FACTT agrees and supports its content. In addition, we have attached recent position paper prepared by our group (Science Translational Medicine 2015), which is an example of hard path for delivery of ATMP to patients in Europe. In the paper we highlight a collaboration between European scientists and regulators including EMA/CAT that allowed for the progress. We hope that the current discussion will additionally push forward this field of medicine.

On behalf of A FACTT members

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Comments to the text:

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.**

A1	• **Line 97-101 Required uniform level of GMP for ATMP**
	  ○ Bearing in mind diversity of therapeutic cells, it is hardly possible to impose common rules covering all ATMPs. In fact, current GMP-compliance in the production of many ATMPs requires compromising the efficacy of the final product (e.g. magnetic separation of impure T regulatory cells instead of flow-based sorting of fully pure ones). When safety of the product can be otherwise provided, new techniques not commonly recognized as GMP-compliant should be approved. It is unacceptable to offer to the patient any cellular product at any stage of its development, while being aware that its quality is poor only because of some bureaucracy. It is of special interest in ATMPs which are usually offered for incurable diseases. It would be therefore necessary to create separate paragraph stating that parts of cGMP requirements can be voided (not only treated 'additionally flexible'), if they consist a significant hurdle for offering novel medicines to the patients, notably for treatments addressing 'unmet medical needs'. This is somehow mentioned in the lines 113-114 but should be more explicit and detailed (for example, acceptance that this waiver in some cases may cover ATMP manufacturing from clinical trial to marketing authorization).
	
	• Line 120-122: It would be desirable to point at particular areas to which this flexibility applies. The areas that delay significantly the development of ATMPs should be the most covered. For example:
	  ○ QC testing of starting materials should rely on CoA
	  ○ Area Classification: Allow fill finish in grade A-in-C (see also A6).

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.
A2	Yes. The risk-based approach should be accommodated to specific activities related to particular products as well as general issues, like sampling of starting materials or testing of final product.
Q3	How should the quality systems established in accordance with Directive 2004/23 be recognized 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?
A3	Cellular product are sufficiently regulated by transplantation legislations as well as cell/ tissue legislations. Necessary GMP requirements are addressed there. There is no reason to make addition distinction for same or different essential function of the cells between the donor and recipient. GMP requirements should be reasonably high for both kind of the cells.

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.
A4	- Line 152-156: As many ATMP-producing companies are small (micro or SME or academic spin-offs), flexibility to the rules of the personnel should be implemented. For example, persons responsible for different roles should be allowed to exchange between different batches of the product, provided this is unambiguously stated in the batch documentation.
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.
A5	• Line 234 and 240: The term 'Large scale production' should be more precise. ATMPs are often produced in the format: single preparation means single batch.
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?
A6	There should be distinction between physical and microbiological clean areas in manufacturing of ATMPs. While microbiological B class is acceptable as a background for A class, physical B class is detrimental for ATMPs both during clinical development and when commercially produced. Physical A-in-C is sufficient to keep the product safe and should be extended to all life cycle of ATMP including commercial purposes, notably when batches of the product are small and only single batch is produced per time (no cross-contamination threat). In many cases of the production of ATMP, B class around A is difficult to be kept because of the specificity of the work with cells and tissues. There should be no simple transition of GMP requirements for small particles to ATMP. Considering commercial ATMPs, keeping A-in-B is also expensive and increase the cost to the patient and health care system without clear impact on improved safety.
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.
A7	If an A-in-C would be sufficient for first-in-man trials, why not extend this also to pivotal clinical trials? This should be applied to both physical and microbiological gradings of A-in-C.
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.)
A8	Yes this should be allowed for. This would have cost and energy saving benefits (see also answer to Q6).
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.
A9	• New types of equipment adapted from the research and development including RUO level should be allowed, provided quality and safety are addressed. This ensures fast translation of basic knowledge with cells into clinical practice with ATMPs.
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.
A10	• Line 338: We fully agree that for investigational ATMPs, sampling and testing of raw materials is not a requirement. In addition, there should be defined transition period allowed at the beginning of commercial manufacturing of ATMP, when testing of raw materials is not a requirement. Again, extensive quality program precludes SME from manufacturing ATMPs
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?
A11	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.
A12	No
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.
A13	• Sampling and testing of each and every container of ATMP for identity is often difficult or impossible. For example, due to the biological content of the preparation (e.g. human albumin or plasma) or low final amount of the batch or product
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
A14	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.
A15	• Line 687: ATMPs are rarely quarantined. In the majority of cases they are not quarantined.
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.
A16	No comment
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.
A17	Validation of the process should allow for variability in the finished product, based on the characteristics of the starting material and establish a proven link between both.

	For a given starting material (cells/tissue), the finished product characteristics should be predictable within a certain range.
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.
A18	• No comments
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.
A19	• Line 938-945: Sampling of starting material may be impossible when low volume is available. In-process material samples or finished product samples should be stored instead in such cases. Long storage of biological materials will be a significant hurdle for SME, consider the storage of documentation only (see also A2). • Line 954: Identity testing of starting materials is not performed for investigational ATMP. • Line 957: 'reference materials' are not available in the majority of ATMP – this definition does not fit at all to ATMP manufacturing • Line 971: Is this also required if it is specified in the applicable SOP and there is only one piece of each equipment? • Line 972 to 973: limited also by small volume per container, sterility and frozen state of most materials.
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.
A20	No comments.
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.
A21	No comments.
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?
A22	Yes
Q23	Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?
A23	Yes
Q24	What activities should, in your view, be considered as reconstitution?
A24	Thawing, washing, counting, diluting, repackaging and mixing
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?
A25	The use of automated devices for the manufacture of ATMPS already exist, eg CliniMACS Prodigy. The benefits will heavily depend on expectations with regard to compliance with computerized systems legislation, typically applied in GMP. If the equipment keeps clinical approval, the personnel of GMP facility (QP) should be responsible for the quality, provided proper training and instructions of use were

	obtained from the device producer and device itself is on-site qualified. When the system is adapted (including RUO as it often happens for ATMPs), it should be allowed too. Quality and safety procedures and responsibility should be then provided by GMP facility personnel, who usually keeps the deepest knowledge on particular manufacturing steps with the equipment.