Good Manufacturing Practice for Advanced Therapy Medicinal Products

Answers to questions Q1 to Q25, as referenced in the text:

General remark.

We support the idea of an ATMP-specific guideline and most of the text is well adapted to ATMPs. The input that we have given is based on the idea that these ATMP guidelines will replace the current GMP guidelines and not replace annex 2. These new guidelines will be applicable to all ATMP classes. Unfortunately, for now it is unclear what the relation with other related documents will be.

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	*The text is well-adapted to the characteristics of ATMPs.* *Line 100-101. The specific manufacturing requirements for investigational ATMPs should be included in this guideline.* *Line 109: include inherent variability of the starting material (e.g. autologous cells)*
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	*We consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the guideline.*
	Examples are:
	- *the use of Media Fills in the ATMP production process:*
	  - *Risk based analysis of the Matrix approach (combined media fills for different ATMP's but based on identical handling of the product).*
	  - *Reduced frequency, based on frequency of manufacturing batches instead of fixed time interval.*
	  - *Allowing risk approaches based on retrospective analysis of production runs*
	- *incoming QC testing of starting materials: no sampling/testing, rely fully on CoA*
	- *Impurities of starting materials to be tested for in release testing based on their associated risk.*
	- *Risk analysis of detection of anaerobic microbiological contamination.*

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 <u>different essential function</u> 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	*We whole heartily agree that the processing of cells for a different essential function can be performed under the EUD 2004/23 quality of tissues and cells*

	and implementing directives. The tissue establishment license and a JACIE accreditation are more than adequate to reduce the risks associated with non-substantial manipulations. *Line 120: While an acceptable level of quality must be ensured for investigational ATMPs, it is acknowledged that additional flexibility is warranted, in particular for early phases of clinical trials. Please define area in which flexibility is warranted.*
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	*The section is sufficiently clear and well-adapted to the characteristics of ATMPs.* *Lines 135-136:* *Maintenance personnel are often from commercial firms. Instead of specific training, instructions and supervision by competent personnel from the facility should suffice* *Lines 141-142: define "affected by an infectious disease"; add 'which could adversely affect the quality of the product' as stated in the GMP regulations*
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	*The requirements are well-adapted to the characteristics of ATMPs.* *Line 213: Accidentally omitted word 'not': 'If sterilisation of the finished product is (not) possible, particular attention should be paid to the filling process'* *Line 234 All HEPA/ULPA filters are Hydrofobic filters. The frame however sometimes is not, and this certainly has its effect on the safety and quality of the filter with possible impact on the product. Therefore we would include air vent filters and frames…. (HVAC)* *Line 234 and 240: The term 'Large scale production' will rarely apply to ATMP manufacturing, even in commercial phase. Also this is very relative. The term could be replaced by 'for clean rooms' in line 234 and removed in line 240 (drains always have to be of adequate size and have trapped gullies).* *Line 234: Validation of a scheduled lifespan is not possible, as it depends on environmental conditions. Periodic verification confirms that they are fit for intended use.* *Could guidance be added regarding the production areas and aseptic environment for the use of fully automated equipment for the manufacturing of CTMPs, such as the CliniMACS Prodigy*
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	*Additional flexibilities are not necessary. The current text allows enough flexibility and allow the production of ATMPs in a safe manner.*

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	*We support the A-in minimal C background for all investigational ATMPs with the exception of gene therapy trials, so for first-in-man trials and pivotal clinical trials.*
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	*Q7 & Q8: Yes, the requirement for a class A cabinet in a class B background may be changed into class A background in a minimal class C background for investigational ATMP's. Validation needs to demonstrate that class A conditions in the biohazard cabinet are maintained during production (by microbiological monitoring and particle counts inside the cabinet). Separation of processing procedures and validated cleaning and disinfection avoids cross contamination and line clearance procedures including extensive cleaning need to be part of the appropriate measures.* *May we draw your attention on a publication available explaning the influence of difference in background on the performance of a laminar air flow cabinet where the increase of risk in quantified..* *(http://link.springer.com/article/10.1007/s10561-012-9355-8)*
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	*The text is well-adapted to the characteristics of ATMPs.* *Line 281: 'Where possible single-use disposable material should be used'. We suggest to add that this material is preferably pre-sterilized/sterile.*
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	*The text is well-adapted to the characteristics of ATMPs.* *Line 317: replace 'medicinal product' for ATMP* *Line 338: We fully agree that for investigational ATMPs, sampling and testing of raw materials is not a requirement.* *Release by exception is a current practice that is unavoidable, and it is very*

	positive that this is described.
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	*Additional flexibilities are not deemed to be necessary.*
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	*Additional flexibilities are not deemed to be necessary.*
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	*Line 473: As different EU legislation result in an unclear situation during handover, we would include that the agreement should include clear definition on responsibilities during handover.* *Line* 486*: remove ' where possible by heat'.* *Line 492: Certain (ophtalmological) ATMPs contain antibiotics as part of the matrix of the finished product.* *Due to the nature of the products and the volume of their recipients, sampling every container and analyzing those samples for identity should not be a requirement. Full analysis of every batch of starting material may be complex due to the biological nature of many starting materials (e.g. mRNA, human albumin, etc).*
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	*The text is well-adapted to the characteristics of ATMPs.* *Line 545-546:* *Delete "where used" or specify that the liquid nitrogen levels should be monitored when the products are stored in liquid nitrogen.* *Line 555: For these banks and stocks we would include the need to provide evidence of working under Dir. 2004/23 or Dir 2002/98 as the absence of this scentence could allow "amnesty" for illegally obtained tissues and cells and reflow from research cell banks. The reflow from research cell banks would be in conflict with Belgian law on Biobanking.*
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 599: When sterilization of articles, materials or equipment is not possible a*

	validated and strictly controlled process is implemented to minimize the risk on processing. *Line 649: When disposable materials are used, cleaning validation is obviously not required. This is not explicit in the text. Add '…unless disposable materials are used'.* *Line 659: 'If possible, media should be sterilized in situ' add 'immediately after preparation'. Small scale media are mostly bought ready-to-use and sterilized by the manufacturer, not by the user.* *Release of ATMP products directly after production may occur by a 2-step process, because not all quality control test results are available (mostly the microbiological test result of the final product). First, the ATMP is conditionally released by the QP on basis of all known test results and subsequently definitively released once the microbiological test results is available. The product is administered to the patient after the first conditional release.*
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	*The text is well-adapted to the characteristics of ATMPs, except for the process validation. See Q17 for a more detailed explanation.*
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. Reproducibility and reduction of process variability should only be targeted when relevant for the product effectivity.* *As stated above, due to limited batch sizes especially during the early stages of development it is very time-consuming and expensive to perform multiple media fill tests. Especially when the clinical study is very small it means that more media fill tests are performed than actual ATMPs being manufactured. Routine procedures for other purposes, such as aseptic media preparation, should show the capability to work according to GMP Guidelines.* *We would suggest that process validation can be incorporated into the validation of the production of the ATMP. Appropriate quality control at critical points during the production and aseptic processing should be included to validate both. This would also alleviate some of the efforts required when modifications to the manufacturing process are made during a clinical study.* *For commercial ATMP production, process validation should include a process simulation test using a culture medium.*
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	*The text is well-adapted to the characteristics of ATMPs.* *Line 767: Since the product complexity of an ATMP is so large the requirements of a QP should be more stringent to ensure that this key person is able to perform the release correctly. We suggest rephrasing: QP must have experience in release of the field of ATMP's and be a qualified for the products they are releasing and prove the detailed knowledge…..* *.*
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	*The text is well-adapted to the characteristics of ATMPs.* *Line 938-943 The current requirements to keep samples of all materials puts a high burdon on low volume production such as ATMP's. It should be possible to reduce the materials affected based on qualification of the material and a risk assessment with impact on the final product.*
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	*The text is well-adapted to the characteristics of ATMPs.*
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	*The text is well-adapted to the characteristics of ATMPs.*
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	*We agree that the manufacturer's responsibility is limited to the production and validation of the process of reconstitution.*
Q23	Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?
A23	*We agree that the principle of reconstitution is not manufacturing and therefore outside GMP.*
Q24	What activities should, in your view, be considered as reconstitution?
A24	*Reconstitution activities are: thawing, diluting in an appropriate buffer and/or rinsing the primary container, washing, centrifugation, mixing and adding of other substances before administration. Where possible, these activities should be performed in a closed system.*
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 text provided within these guidelines provides the necessary flexibility to encompass the production of ATMPs in automated devices. Although automated, a QC should be responsible for validation of the procedure and all necessary quality control tests. A QP should still release the final batches of products.*