Good Manufacturing Practice for Advanced Therapy Medicinal Products

Response on behalf of members of the ATMP-working group in the Netherlands and Belgium

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General remark.

We support the idea of an ATMP-specific guideline and most of the text is well adapted to ATMPs. Our input is based on the idea that this ATMP guideline will replace the current GMP guidelines and not replace annex 2. This new guideline will be applicable to all ATMP products (any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products, tissue engineered products and combined ATMPs). 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.*
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*
	- *QC testing of starting materials: no sampling/testing, rely fully on CoA*
	- *Testing of impurities of starting materials based on their associated risk.*
	- *Allow risk based approaches for testing 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 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	*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. Identical methods are applied for processing of bone marrow for hematopoietic stem cell transplantation and for other essential functions. Processing of these non-substantially manipulated ATMP in LAF cabinets (grade A) in minimal class D environment is safe.* *The JACIE accreditation system is based on peer-review, and has standards for an extensive quality management system. These standards definitely go into more detail than the current ATMP specific GMP guidelines. The JACIE Manual is extremely informative, for centers as well as inspectors and the JACIE checklist is available for self inspection (http://www.jacie.org/home).* *In our view, the potential risk for the patients receiving cells for a different essential function is not to be attributed to the processing procedure, if this is being performed under the EUD 2004/23.* *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 external 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* *Line 144-146: delete personnel engaged in taking care of animals. This activity should not be done by the same staff or in adjacent areas. In addition, vaccination is a personal decision and cannot be imposed on staff members, but only encouraged.* *Paragraph 147- 151: Add to the sentence: if such passage is unavoidable… a risk assessment should be performed.*
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 172: Replace 'Medicinal Products' by 'ATMPs' *Line 198: Rephrase: should minimise the risk of confusion between different medicinal products or their components.* *Line 202: The "laid out" should be replaced by "lay out" or design* *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: 'HVAC' should read 'HEPA' to be more correct, since HVAC systems may also contain non-HEPA filters* *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.* *Line 246: 'Clean areas grade A, B or C' instead of 'clean areas', since grade* D *areas typically may have drains and are also clean areas.* *Line 266: In process controls will typically happen in production, and will therefore be done in production areas.* *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 D background for all investigational ATMPs, 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 D background for investigational ATMP's. Validation needs to demonstrate that class A conditions in the LAF cabinet are maintained during production (by microbiological monitoring and particle counts inside the cabinet) and class D should also be maintained. Separation of processing procedures avoids cross contamination and line clearance procedures need to be part of the appropriate measures.* *§ 4.2:* *Please include a paragraph on premises requirements for "completely closed" manufacturing processes such as the CliniMACS Prodigy and the use of bioreactors for the production of ATMPs. We suggest allowing flexibility for these types of manufacturing (see Question 25).*
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 adding 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 327: include the IMPD to be taken into account for each new version of specifications.* *Line 338: We fully agree that for investigational ATMPs, sampling and testing of raw materials is not a requirement.* *Line 388 to 398: Shouldn't there also be an acceptability statement made regarding the received material?* *Line 417 to 419: Release by exception seems far off in today's ATMP manufacturing reality. Currently, this paragraph can be left out.*
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 456: add 'and Directive 2006/17/EC'* *Line 464: Replace the word 'supplier' with 'material' as there are rarely specifications set for a supplier.* *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).* *Lines 511-514:* *We disagree with: "The initial non-substantial processing of cellular starting material has to take place in accordance with the pharmaceutical rules". This is impossible, e.g. for ATMP produced from frozen umbilical cord blood (UCB) as starting material. The UCB product that is used as cellular starting material for ATMP is often processed and stored by a Cord Blood Bank that has no GMP license but has been accredited by Netcord/FACT. Directive 2004/23/EC regulates the donation, procurement, testing, processing, storage, preservation, storage and distribution of all human tissues and cells intended for human application. Non-substantial manipulation of human tissues and cells preceding the start of the ATMP production process may therefore be executed by a licensed Tissue Establishment. The responsible person of the Tissue Establishment releases the non-substantially manipulated cell product either for direct application on humans or for further processing into an ATMP.*
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 recorded when the products are stored in liquid nitrogen.*
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 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.* *Line 675: Replace 'irradiated equipment and materials' by 'ionizing radiation in the manufacturing of ATMPs'.* *Line 687: Due to the extremely short shelf life of some ATMP's, these are not put in quarantine in a physical nor in an administrative manner*. *Release; lines 687-689, 731-733 and § 11.3.2 appear to be contradictory.* *Release of ATMP products directly after production may occur by a 2-step process, because not all quality control test results are available at time of release and administration (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 are available. The product is administered to the patient after the conditional release. This procedure is reminiscent of the procedure that is used for the release of freshly processed hematopoietic stem cell transplants by Tissue Establishments. In our opinion, lines 687-689 and 731-733 do not allow a 2-step release procedure in which the investigational ATMP is already administered to the patient after the first release step, whereas § 11.3.2 does.* *In section 9.7 it is stated that reprocessing of rejected material is only allowed when this does not affect the final product and follows written predefined procedures. Although we do agree this should be aimed for, it might prove difficult if not impossible to test for when no functional tests are available or the exact mode of action of the ATMP is unknown.* *Furthermore, for some patients the only possibility for treatment is an ATMP from autologous material. In case the starting material does not meet all release criteria, rejecting it means that the patient cannot be treated. In such instances it should be possible to manufacture the ATMP after consideration of the risks involved and should be an exceptional release with clear communication to the responsible physicians.*
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.*

	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 small numbers of patients are included in the clinical study, 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 734- 737: Safeguards against the release of uncertified materials for investigational ATMP: is it deemed sufficient that the person delivering the ATMP waits for the certification before issuing it to the clinic?* *Line 836 seems in contradiction with line 831 with regard to the use of a register.*
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 928 and 931: samples should be 'taken' instead of 'kept'* *Line 928 to 932: For investigational ATMP, sampling of starting materials is not a requirement either. Please specify.* *Line 954: Identity testing of starting materials is not performed for investigational ATMP.* *Line 957: Section 10 does not specify the expectation on validation of testing methods. Remove '(see Section 10)'.* *Line 971: Is this also required if it is specified in the applicable SOP and there is only one piece of 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	*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. However, we do feel that the manufacturer of ATMPs should be encouraged to verify that appropriate facilities and trained personnel are available in institutions where the ATMP is reconstituted.*
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.* *The only flexibility which we would suggest is to place the automated device in a dedicated unclassified room. Automated devices for the manufacture of ATMPs, (eg CliniMACS Prodigy) are already available. The flexibility will also depend on compliance with just the ATMP specific GMP guideline or with other legislation such as computerized systems legislation*.