Comments by the Antwerp University Hospital (UZA, Antwerp, Belgium) on:

Good Manufacturing Practice for Advanced Therapy Medicinal Products

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Date issued: October 15th, 2015

Answers to questions Q1 to Q25, as referenced in 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 120-122: Could you indicate to which areas this flexibility applies? We believe it could apply as follows:
	  ○ Incoming QC testing of starting materials: No sampling/testing, rely fully on CoA
	  ○ Media Fills: Matrixed approach, combined for several ATMP's but including all activities. Reduced frequency, based on frequency of manufacturing batches instead of fixed time interval.
	  ○ Area Classification: Allow fill finish in grade A-in-C for phase I and II clinical trials.

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	Additional detail would be welcome. The risk-based approach can be used on Media Fill (excluding incubation steps since no risk of contamination), incoming starting material QC sampling (small sterile and or frozen recipients would no longer be fit for purpose after sampling) and impurities to be tested for in release testing based on their associated risk.
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	GMP compliance should not be required for cells/tissues, solely because they are used for a different essential function. Compliance with cell / tissue bank legislation covers this. E.g. Concentrate of autologous bone marrow mononuclear cells (BM-MNC) intended for improvement of heart function (LVEF) and quality of life in patients with ischaemic post acute MI and in chronic heart disease.
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. • Line 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	• Line 172:Replace 'Medicinal Products' by '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: '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: IPC testing will typically happen in production.
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	No
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?
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. Environmental Monitoring data should support the grade A classification of the filling area. This would have cost and energy saving benefits.
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	• 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	• 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	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	We suggest not to have a separate certificate of conformity.
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	• 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). • 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.
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 571: Changes in the manufacturing requirements. Isn't this also again considering substantial changes? • 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.
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	• 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. • Line 850: Is delegation of QP duties not in conflict with Annex 16? The whole concept of delegation of release activities as currently expressed in the document, is unclear.
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 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 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	Yes, 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	Yes, 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 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.

General remarks

G1. Segregation between investigational and commercial ATMP
The consultation document should be more transparent on which expectations actually apply to investigational ATMP and which ones are only applicable to commercial ATMP.
Maybe a further split-up between first-in-man and pivotal clinical trial ATMP's can be made.

G2. Required level of GMP in early phase clinical trials.
In the US, manufacturers are exempt from many of the GMP requirements specified during phase I trials. This introduces unfair competition in scientific progress.