EUROPEAN BLOOD ALLIANCE

Unit B5 – "Medicinal products – policy, authorisation and monitoring"
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European Commission
DM24 02/133
B-1049 Brussels (Belgium)

Amsterdam, 22 September 2016

Dear Sir/Madam,

Targeted stakeholder consultation on the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products

On behalf of European Blood Alliance (EBA) we thank DG SANTE for the opportunity to contribute to the "Draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products".

Information of the contributor

The European Blood Alliance (EBA) is an association of 25 not-for-profit blood establishments in the EU and EFTA. Our mission is to contribute to a safe, sustainable and affordable blood, tissues and cells supply for Europe. EBA is registered in the Transparency Register with the Identification number in the register: 149855010621-40.

We have circulated this document for comments to the members of EBA and discussed those within the EBA Tissues and Cells Working Group. Attached please find the contribution of EBA based on this consultation process.

General comments

As a whole the draft document reflects the current knowledge of the ATMPs and takes into consideration that the manufacturing of ATMPs and the expertise needed differs significantly from that of traditional pharmaceuticals.

We appreciate that principles of EU GMP guidelines have been introduced to this guideline. It is however not clear how this document should be interpreted in relation to EU GMP Guidelines. Specifically we feel that it is important to clarify whether national Competent Authorities will inspect against this document or the EU GMP Guidelines and ATMP regulations and also how this guideline will be kept updated in respect of changes in the latter. We are concerned that potential discrepancies or elements of detail not captured in the summary will lead to inadvertent non-conformances by the types of non-specialist organisations the Guidelines are designed to help and suggest that the Guidelines would be better placed as an annex linked to Eudralex volume 4 and cross-referenced to that and other documents where appropriate.

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Specific comments

Specific comments to the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products are presented in the table below:

Lines	***Comments***
Lines 144/ Risk Based approach	*A risk based approach is welcomed however care should be taken when applying this. Reference to, ICH Q9 and Human Cell Based Medicinal products EMA/CHMP/410869/2006 should be specified.* *Examples of risk based approach are welcomed.* *Direction regarding autologous products and acknowledgement that finished products may have a degree of variability is welcomed.* *It is welcomed that a compliance with GMP should be ensured regardless of the manufacturer.*
Lines 255---257	*This sentence needs additional explanation. Should a traditional approach for process validation replace the routine batch testing? Should a continuous verification approach be more appropriate?*
Lines 300-302	*It is defined that under no circumstances it is acceptable to conduct manufacturing in premises with air quality classification lower than a critical clean room of grade A in a background of grade D.* However, lines 2171-79 (automated production, closed system) state that manufacturing in controlled but non-classified background environmental is acceptable. This contradiction should be corrected in the text.
Lines 320-340	*Re lines 320-340 we would recommend reference to closed and open processing as part of risk or whether Grade A with C background is acceptable.* *Further in the document there is reference to the use of isolators with grade D background, it would be better if this was considered in this section.*
Line 324	*Define "separation of processing procedures".*
Line 325	*Replace "validated cleaning and disinfection are put in place" by "validated cleaning and disinfection procedures are in place".*
Line 329	*Why an appropriate frequency of "calibration, inspection or checking" should be on annual basis? In the chapter 3 of GMP as well as in this document ---lines 670---671--- a "defined intervals" is recommended. A risk analysis approach should be expected to all equipment used, not only in order to reduce the frequency of the controls to the "rest of equipment".*
Line 342/ Personnel	*Much of this section is a repeat of GMP annexes and they should be cross referred to. While it is accepted that it is not always possible to fulfil all roles in a small organisation, care should be taken to draw a line between production and QC management.*

Line 435/ Premises	*This would be better as an annex of Eudralex volume 4, there is much repetition of annex 1.*
Lines 462-463	*Being investigational ATMPs less known in terms of quality and safety (see lines 190---211) with respect to authorized ATMPs (that should be produced in a dedicated area of the facility) it seems inconsistent to accept that they can be manufactured in the same multipurpose area of a medicinal product other than ATMPs.*
Line 547	*Replace "incidents" by "air device failure".*
Lines 587-588	*We suggest mentioning "bacteria, yeast, moulds, etc.".* *It is not clear the meaning of "host organism"; moreover, it is unlikely to found anaerobes (bacteria) in the environment.*
Lines 591-592	*This sentence should be clarified or "may be adapted after validation of the premises" can be replaced by "may be adopted in routine monitoring only after clean room and clean air device classification".*
Line 650/ Equipment	*This would be better as an annex of Eudralex volume 4.*
Line 691/ Documentation	*Nothing to comment other than there is much repetition of Eudralex Volume 4.*
Line 880-914/ Traceability	*As regard the traceability of blood and blood components and if deemed appropriate reference to the*
Line 915/ Starting and raw materials	*Use of research grade material must include robust risk assessment.*
Line 1134/ Production	*Nothing to comment other than there is much repetition of Eudralex Volume 4.*
Line 1551/ Process validation	*If comparing chapter 10.3 with lines 255-257 and lines 1624-1631, it is understood that process validation (three consecutive batches under routine conditions) only applies for market authorized ATMPs. This could be specified clearer in the afore mentioned chapter.*
Line 1645/ Qualified person and batch release	*Reference to the release of ATMPs under the terms of a manufacturing specials licence (where allowed) should be made.*
Line 1854-1862/ Sampling	*General principles: Does this chapter apply for all manufactured ATMPs despite developmental phase? If a gradual increase in the sampling requirements also applies for this chapter, it could be specified in more detail. It seems quite exhaustive to conduct sampling according to the current guideline for e.g. first-in-man ATMPs.*
1881-1927	*The requirement to retain samples from raw materials, starting materials, active ingredients plus intermediate products in addition to final products and packaging for 2 years seems onerous.*

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Lines 1892-1894	*It has been defined that reference samples are not required in the case of autologous ATMPs and certain allogenic ATMPs (matched donor scenario). It is not clear if the matched donor scenario for allogenic ATMPs is presented merely as an example or is it the only case where reference samples are not required for allogeneic ATMPs? There are also a large variety of other allogeneic ATMPs, where the amount of the starting material is limited. For the sake of clarity this particular point could be further specified.*
Line 2002	*Welcome the detail on lines 2002 re highly specialised testing labs.*
Line 2023/ Quality defects and product recalls	*Detail regarding situations where a product cannot be recalled is helpful.*
Line 2074/ Reconstitution of product after batch release	*Examples are welcomed.*
Line 2116/ Automated production of ATMPs	*We do not feel there is enough clarity around the section of automated ATMPs, particularly in the release of the ATMP.* *Examples should be given.*

EBA is committed to advance safe and secure supply of substances of human origin, including ATMPs, in Europe and would like to contribute to the development of up-to-date and appropriate regulations for the benefit of donors and patients.

Should you need some further clarifications or additional information please contact us or the EBA Office at info@europeanbloodalliance.eu.

Yours sincerely,

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Chair, Tissues and Cells Working Group
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