Comments on
Consultation Document: Good Manufacturing Practice for Advanced Therapy Medicinal Products

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Comments provided below are limited to those areas whereby Voyager believes additional language/clarity is needed to respond to the EC query. Questions whereby Voyager has not provided comments may be construed as concurrence with the EC.

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.

The requirements laid down in Section 4 appear to have been overly adapted for the production of ATMPs. There are instances where the language used is subjective, is not open to interpretation and does not add any value. Such as the use of "carefully" in line 169 and "maximum" in line 174.

There a number of instances where the procedures requested are not feasible, have mixed concepts, or are unrealistic given the setting for example: lines 193-194 ask for decontamination of the heating, ventilation and air condition systems; lines 234-235 refer to " air vent filters (HVAC)" and state they should be "validated for their scheduled life span". It is assumed lines 234-235 are actually referring to vent filters on vessels not filters used within HVAC systems. As currently worded it could be misconstrued that the intent is to validate the life of filters in HVAC systems, which we believe is not the intent. A further example, is lines 237-238, it is agreed airlocks "should" be used to access cleanroom area, yet within certain settings such as hospital or academic it is not reasonable to expect or demand they be interlocked.

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?

Yes, while reasonable to expect some level of decontamination of facilities to support a multiproduct approach, requirements such as decontamination of the HVAC system actually reduce flexibility. With appropriate process controls such a need would be moot. Likewise procedural controls can be used for airlocks without the need for interlocking systems.

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.

Yes, the language used for premises should be more flexible, for a number of initial (first in man) clinical trials, ATMPs are generally produced in hospital or academic settings and the premises at these sites most likely do meet the strict requirements detailed in this section. The use of more flexible language with regards to the premises in which the ATMP is manufactured in particular for first in man trials will not in any manner impede its quality, provided adequate controls are utilized. Ideally GMPs for investigational ATMPs should be structured along the lines of those described for biological products. Only where there is specific knowledge or experience which may prevent a potential safety issue should greater details or expectations be provided. Some of the proposals within this document establishes higher and potentially

different standards /expectations than in the other established GMP Guidelines. For examples the section on TSE/BSE goes above and beyond the current European Directives.

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.)

Generally aseptic areas are not used for the entire manufacturing process. Rather their use should be dictated by the given state of the process and the potential risks to the process or safe use of the product. For the final processing steps of the finished product aseptic techniques and facilities need to be considered where the finished product cannot be terminally sterilized. For commercial ATMPs inclusive of gene therapy products at the finished product stage, it is reasonable to require that one comply with the aseptic processing guidelines. For first in man clinical product manufactured in either a hospital or academic setting it may not be possible to have full compliance especially as relates to Grade A within Grade B. Rather a more reasonable expectation is for Grade A within Grade C. Appropriate environmental controls need to be exercised and media qualifications need to demonstrate that product can be aseptically produced under such conditions. In earlier process steps the expectations for the environment and its controls should be the same as those applied for biologics given the levels of similarity in terms of cell culture and purification.

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.

The requirements laid down in Section 5 are generally well-adapted to the specific characteristics of ATMPs with the exception of line 278, “equipment that come in contact with product must not be reactive, additive or absorptive”. It is recommended that “must not” be changed to “should not”. In early stages of product development it is generally not known if product is reactive, additive or absorptive. This information is typically assembled during the development process.

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.

In general the requirements laid down in Section 7 are well-adapted, however there are major inconsistencies in this section. The section points to the appropriate European Pharmacopoeia (Ph. Eur.) Chapter for overall quality of the raw materials and to the appropriate Directive for

procurement and testing of human tissues. However for Transmissible Spongiform Encephalopathy ('TSE ") the section lays down the requirements. The overall quality of the staring and raw materials including "TSE" should be based on the Ph. Eur. general monographs and appropriate Directives as these are legally binding. Hence requirements with regards to "TSE" should reference Ph. Eur. Chapter 5.2.8: Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

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.

The requirements laid down in Section 8 are generally adequate. However there are a few instances where procedures requested may not be feasible/applicable and/or are deemed unnecessary for example line 545 where it requested that "the liquid nitrogen level be monitored".

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.

The requirements laid down in Section 9 appear to have been overly adapted for the production of ATMPs. It is suggested that this section have a preamble that indicates that the development of a product is phase dependent and procedures and quality controls will become more refined and detailed as development progresses. It is agreed that the production of ATMPs should follow appropriate and adequate controls for cleanliness, prevention of contamination and sterile operations. However a number of procedures detailed in this section tend to be over exacting and not necessary. For example: l) line 645 "manufacture of different viral gene therapy vectors in the same room is not acceptable". Manufacture of different viral vectors should be separated by space/time and appropriate controls and not by area. The overall goal is to prevent contamination yet allow for flexibility and more efficient and cost saving production. This does not require dedicated rooms. 2) lines 659-661 "If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, etc. to bioreactors should be used where possible." In-line filters should be used only where appropriate and feasible. It is not feasible to use in-line filters at each step and often other sterilizing techniques can be used just as effectively.

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?

Yes, it is agreed that if the 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 via appropriate means.

Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?

Yes reconstitution is not manufacturing and should not be subjected to GMP regulations.

Q24: What activities should, in your view, be considered as reconstitution?

Reconstitution should be viewed as any manipulation that occurs to the finished ATMP at the site (locale, e.g, hospital, treatment center, doctor's office, patient's home, etc.) of administration.