RESPONSE TO THE TARGETED STAKEHOLDER CONSULTATION ON THE DEVELOPMENT OF GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCTS PURSUANT TO ARTICLE 5 OF REGULATION 1394/2007

Date of Response: 11 November 2015 FINAL

Stakeholder: Dimension Therapeutics, Inc.

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1 STAKEHOLDER INFORMATION

Stakeholder: Dimension Therapeutics, Inc.

Activities: Research and Development

The company falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50million annual turnover and fewer than 250 employees).

2 COMMENTS RELATED TO THE QUESTIONS

2.1 GMPs for ATMPs: General Principles

Question 1: 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.

The principles laid out allow for flexibility and allow for a case-by-case review of the processes for manufacture of both commercial and clinical ATMPs. However, Section 2 places more focus on the manufacture of clinical ATMPs and further information on the flexibility allowed for the approach to the potential scale up and subsequent manufacture and control of commercial ATMPs could be added.

The draft guideline states:

91 there is a quality control system which is independent from production

Please clarify if the quality control system encompasses quality assurance?

97 No provision in the GMP Guidelines (including the risk-based approach) can be regarded as
98 derogation to the terms of the marketing authorisation or clinical trial authorisation

Consider rewriting the sentence as "this guideline does not supersede the conditions specified in the marketing authorization or clinical trial authorization"

Question 2: 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.

The information provided in the section on the risk-based approach is very high level with no specific examples provided. This might be the best approach given the varying nature of ATMPs. However, if further examples could be added, this section could be split down into the different types of ATMPs to allow for more clarity to the ATMP manufacturers.

The draft guideline states:

103 ATMPs are complex products and risks may differ according to the type of product. For
104 example, the risks to the quality of the product are greater when there is a complex
105 manufacturing process.

In some aspects, the manufacturing from some ATMPs could be considered to be quite simple consisting of a fermentation process, albeit with the addition of complex raw materials, with a minimal purification process. It is the more simple processes that result in a higher risk and more need for a risk-based approach. The need to control the microbiological and viral safety of all raw materials of animal and human origin is more important because of the lack of clearance steps. The TSE risk can still be managed in the same way as applied to the control of all products manufactured with raw materials of animal and human origin.

In addition, the cell expansion processes for cell-based ATMPs often employ the use of complex growth factors etc., many of which are manufactured for research purposes only. Because of the minimal purification steps, residual levels of these proteins may remain in the finished products. Approaches to dealing with these issues could be discussed in the guidelines.

Comment on the text:

103 ATMPs are complex products and risks may differ according to the type of product

ATMPs are complex products and risks may differ according to the type of product and intended use

104 For example, the risks to the quality of the product are greater when there is a complex
105 manufacturing process

Consider rewriting as "risks to the quality of the product may increase with increasing complexity of the manufacturing process"

Question 3: How should the quality systems established in accordance with Directive 2004/232 be recognised 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?

The question revolves around the definition of 'substantial manipulation', and this requires additional input from the commission. The JACIE accreditation system details recognised requirements for haematopoietic stem cell collection. If the processes start point for stem cell isolation is defined as donor collection then other than stem cells obtained from umbilical cord, it is difficult to describe this process as not involving substantial manipulation.

2.2 Personnel

Question 4: 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.

Overall, the measures are appropriate and in keeping with general GMP practice.

The draft guideline states:

140 Steps should be taken to ensure that health conditions of the personnel that may be relevant to
141 the quality of the ATMP are declared.

Conversely, there is the possibility when manufacturing autologous cell therapy products that the patient may be carrying a viral infection. Appropriate measures are outlined for protecting the personnel but the risks and monitoring of the personnel should be more clearly outlined.

GMP and health hazard considerations should not be confused. One focuses on product quality and the other focuses on operator safety. Recommend to paraphrase from ICH Q7 with regard to GMPs. Health hazard considerations should be handled according to the known risks of the ATMP as for any medicinal product.

2.3 Premises

Question 5: 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 draft guideline states:

185 … In particular,
186 to protect the operator and the environment, dedicated production areas should always be used
187 for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).

It is unlikely that pathogenic organisms will be used as with the ATMP or for the manufacture of the ATMP; it would be more typical to use an attenuated strain. Therefore, this provision may not be necessary.

It is more likely that in the case of autologous cell therapy products, there will be a risk of viral contamination from the subject and this should be considered in terms of room classification. For other ATMPs, a risk-based approach to the environmental classification should be taken. This approach is appropriately detailed in the guideline.

202 laid out

should read "layout"

The draft guideline states:

212 … If
213 sterilisation of the finished product is possible, particular attention should be paid to the
214 filling process.

It is unlikely that any ATMP finished product could be sterilised and therefore more attention should be placed on aseptic filling processing where sterilisation is not possible. However, this might be a typographical error and it is possible that the guideline should state "If sterilisation of the finished product is NOT possible, particular attention should be paid to the filling process". Can this be clarified?

In addition the draft guideline states:

214 For commercial production of ATMPs, the premises should be fully
215 validated.

More detail about the meaning of facility validation would be helpful OR reference the appropriate GMP guidelines

Question 6: 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?

Where patient samples are utilised for autologous treatments, testing and potential segregation of individual 'manufacturing areas', based on any positive screen results, needs to be considered within the facility design.

Question 7: 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.

Because of the safety risk to the patient, similar requirements for manufacturing premises should be in place for manufacture of product for first-in-man clinical trials and pivotal clinical trials. The guideline as written allows for the flexibility required for the different manufacturing scales.

Question 8: 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.)

It should be clarified why gene therapy products are considered an exception in Q8. There may be areas where the manipulations will be conducted in enclosed bioreactors or biological safety cabinets, where a risk assessment could be conducted to identify the control mechanisms. However, it is difficult to see why, if grade B background air is a requirement for pivotal clinical trials and commercial production, it should not be a requirement for early stage clinical trials.

2.4 Equipment

Question 9: 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.

Section 5 discusses the use of multi-use equipment and the need to validate the sterilisation process. Cleaning should also be considered in this section to ensure no carry-over of contaminants other than the ATMP. Appropriate risk-mitigation measures commensurate with the risks should be implemented to prevent cross-contamination with the product and will other raw materials and reagents.

Consideration should be made for analytical time lines to confirm any out of specification for air and/or water monitoring.

Developers and manufacturer of ATMPs should be encouraged by the Commission to utilise techniques that can provide rapid results, especially when involved with products that may have short shelf life and are therefore likely to be released on a conditional approval.

2.5 Documentation

Question 10: 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.

The draft guideline states:

301 quality assurance system

Here quality assurance system is explicit, but earlier and later (Section 12) in the document it seems to be incorporated with a larger quality control system. If these two systems are to be differentiated, it should be explained.

The update to the retention of batch records is in line with FDA recommendations, but not with TGA guidelines. The language is very general and would benefit from some clarification of whether there are any differences in requirements for drug substance and drug product.

Question 11: 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?

It is not considered additional flexibility is applicable in this area.

Question 12: 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.

Yes – differences between first in man clinical trials and pivotal clinical trials should be considered.

The draft guideline states

332 substantial modifications in the manufacturing process of an investigational ATMP also
333 require approval by the competent authorities

Does this approval have to take place prior to implementing the changes? Pre-approval is arduous for early phase development of an investigational ATMP. During the early phases of development, manufacturing process changes are necessary and should be anticipated. It would be helpful if you could comment or provide guidance on early phase development.

2.6 Starting and Raw Materials

Question 13: 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.

The risk of contamination of starting and raw materials should also take viral safety into account as the manufacturing process may not include appropriate viral clearance steps.

Starting material for autologous treatments will present additional challenges in terms of controlling and determining any existing contaminants against any introduced agents.

This section (7) would benefit from being separated into the appropriate categories: DNA/plasmid gene therapy products, viral gene therapy products, bacterial vs mammalian cell therapy products, etc.

2.7 Seed Lot and Cell Bank System

Question 14: 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.

Viral seed stocks, together with production and analytical methods used should also be considered in this section. Viral seed stocks and cell banks are starting materials for viral gene therapy products so it makes sense to have this section be a sub-section of the above Starting Materials Section (7)

2.8 Production

Question 15: 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.

Most ATMPs involve cellular material and so the reference to aseptic manufacturing which is defines as sterile processing is misleading from a regulatory and process point of view.

2.9 Qualification and Validation

Question 16: 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.

In most cases, the manufacturing process for ATMP products could be considered to be a non-standard process and some National Competent Authorities may expect to see aseptic process validation in the IMPD even for first-in-man trials. A risk-based approach should be implemented with regards to the need for process validation and this should be clarified within this guideline.

Question 17: 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.

Biological variability should not be inherent within ATMPs. Variability is typically caused by poor understanding of the critical quality attributes and process parameters used to control the parameters that are considered variable. It should be possible to validate reduced volume analytical tests so providing sufficient production material for patient treatment, or to fully validate at an early stage and perform a statistical approach to reduce the requirements for batch sampling.

2.10 Qualified Person and Batch Release

Question 18: 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.

For products with short shelf life it may be necessary to release product under quarantine if all necessary batch release testing, i.e., sterility, has not been completed. This should be discussed with the appropriate risk analysis and control plan for any lot failures.

2.11 Quality Control

Question 19: 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.

The requirements are sufficiently well adapted in this section

2.12 Outsourced Activities

Question 20: 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.

There is no discussion of continuous assessment and audits based on a risk approach to any outsourced supplier that would be expected as part of a Quality Management System (QMS).

2.13 Quality Defects and Product Recalls

Question 21: 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.

Short life products may have been used prior to a product recall, so an action plan for remediation and monitoring may be more appropriate.

2.14 Reconstitution of Product after Batch Release

Prior to administration to patients, ATMPs may require certain additional steps after they have been released by the QP of the manufacturer. These steps are generally known as "reconstitution". Examples of reconstitution include thawing, dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes). Reconstitution is typically conducted in a hospital.

Question 22: 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. In addition the manufacturer, or more accurately the clinical trial sponsor or Marketing Authorisation Holder, should ensure appropriate continuous training and verification is in place at the site of reconstitution to ensure that the safety of the patient is ensured. This will include annual training of personnel, tracking of any generated data, trend analysis, etc.

Question 23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?

Yes, Within the definitions provided in the guideline, we agree that reconstitution is not manufacturing and therefore is outside GMP. However, the reconstitution process should be well documented and should take place in suitable premises with suitable containment where required. Appropriate training and personnel monitoring should also be in place.

Question 24: What activities should, in your view, be considered as reconstitution?

The definitions provided within the guideline (thawing, dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes)) are appropriate. In addition, simple centrifugation and resuspension steps could also be considered to be reconstitution.

Any steps involving cell expansion or growth and recovery should not be considered as reconstitution but should be considered as manufacturing steps requiring GMP and QP release.

2.15 Automated Production of ATMPs

Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges.

Question 25: 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?

GMP obligations should start with the equipment vendor. A potential purchaser would expect to provide a design qualification, with the vendor providing the installation, operation and potentially

production qualification documents, prior to equipment sign off and introduction into a manufacturing facility. In addition, the institution (ie hospital) should be responsible for the validation and periodic maintenance of the automated devices/systems"