**Consultation Document: GOOD MANUFACTURING PRACTICE FOR ADVANCED THERAPY MEDICINAL PRODUCTS**

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**Submitted by:**

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***Activities*: Clinical Research Organisation**

Dear Sir/Madam,

Please find below comments from the Advanced Therapy Forum on behalf of PPD on the targeted stakeholder consultation on the draft Guidelines on Good Manufacturing Practice for Advanced Therapy Medicinal Products.

PPD does not fall within the EU definition of a small and medium-sized enterprise and currently is not registered in the Transparency Register.

The table below only lists the sections for which comments are provided. Lines in the consultation document to which the comments are related to are included for clarity purposes.

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| **1. Introduction** |
| Line 103 | Include reference to MA Holder and Clinical Trial Sponsor as well as the manufacturer in relation to ATMP manufacture and pharmaceutical quality system. |
| **2. Risk-based approach** |
| 2.2. Application of the risk based approach by ATMP manufacturers |
| Line 172 | Include reference to MA Holder and Clinical Trial Sponsor as well as the manufacturer in relation to ATMP manufacture and pharmaceutical quality system. |
| Line 177 | It should be specified that the additional measures to be put in place to address the specific risks of the product or the manufacturing process should be documented in the form of a risk assessment. |
| Lines 191-197 | When considering the risk based approach, all the parties involved should be informed – it should be specified that 3rd party vendors need to be aware of the measures put in place by having access to the risk assessments. The full supply chain should be aware of the strategy designed (from bench to bedside). |
| *2.3.4. Additional considerations specifically relevant for investigational ATMPs* |
| Lines 320-321 | It would be helpful to have a list of acceptable flexibilities for early stages of development. |
| Line 322 | For this example, it should be indicated that the risk-analysis study should indicate an increased amount and frequency of environmental monitoring and cleaning. It should also include increased cleaning validation studies and room decontamination. |
| Line 328 | For equipment not used frequently, the risk assessment should include steps like short performance qualification or performance tests prior to use. |
| **3. Personnel** |
| 3.2. Training |
| Line 352 | Required training should be flexible and aligned with the risk-based approach, depending on batch size and shortage of materials. The possibility of concurrent training validation and competency could be added (related to line 1601). |
| Lines 359-360 | Reference should be made to product GMO risk assessment and applicable environmental agency approval for product manipulation. |
| 3.3. Hygiene |
| Lines 402-408 | Flexibility in requirements should be dictated by environmental monitoring trends and should be justified and documented. |
| **4. Premises** |
| 4.2. Production areas |
| *4.2.1. Design and construction* |
| Lines 461-465 | It needs to be included that his approach needs to be supported by a risk assessment and the implementations of appropriate control mechanisms. |
| Lines 472-474 | The thorough cleaning and decontamination procedure should also be supported by a risk assessment based on ATMP type. |
| *4.2.2. Aseptic environment* |
| Lines 525-526 | Add flexibility for filling in clean room of grade A with a background clean room of grade C, provided that proportionate controls and environmental monitoring are included in an extensive risk-assessment during the filling qualification phase. |
| *4.2.3. Environmental monitoring* |
| Lines 549 and 593 | An additional factor to be taken into account to determine the frequency of monitoring is the criticality of the procedures/manipulations that take place during the manufacturing process (higher frequency of monitoring for more critical steps). |
| Line 603 | Indicate level of excess of the limit to trigger different actions: from excursion review to formal investigation and CAPA plans. |
| 4.4. Quality control areas |
| Line 638 | Recommend to specify “Quality control laboratories” instead of “Control laboratories”. |
| 4.5. Ancillary areas |
| Lines 648-649 | A restriction in movement between facilities handling animals should be implemented based on a risk based approach. |
| **5. Equipment** |
| 5.2. Maintenance, cleaning, repair |
| Lines 685-689 | The appropriate measures that need to be applied to avoid the risk of cross contamination should be supported by a risk assessment. |
| **6. Documentation** |
| 6.2. Specifications and Instructions |
| Lines 710-715 | It should be mentioned that it is recommended to refer to applicable Eur. Ph. Monographs for setting specifications (e.g. Ph. Eur. 5.14 Gene transfer medicinal products for human use). |
| Line 786 | Reference to Annex 13 should be included. |
| Lines 787-791 | Recommend to include: All changes should be captured/evaluated using change control processes and versions of documents controlled using document control practices. |
| 6.4. Other documentation |
| Line 847 | “Maintenance and calibration of equipment” should be changed to “Maintenance, calibration and servicing of equipment”. |
| Line 848 | Cleaning validation studies should be added to the list. |
| **7. Starting and raw materials** |
| 7.2. Raw Materials |
| Line 931 | Recommend to include classifications of raw material, critical raw material and starting material. Reference to the proposed monograph (Ph. Eur 5.2.12 *Raw materials of biological origin for the production of cell-based and gene therapy medicinal products*) or any future guidance should be made. |
| 7.3. Starting Materials |
| Lines 987-988 | Quality requirements for starting materials should be agreed and documented by the ATMP manufacturer. |
| **8. Seed lot and cell bank systems** |
| Line 1072 | Recommend to modify to indicate that if the establishment of working seed lot/cell banks is not feasible/not mandatory, a risk assessment should be completed and this should be documented. |
| Lines 1130-1133 | It should be indicated that sponsors need to understand that the responsibility lies with the manufacturer and it is expected that sponsor provide the history of the cell line and collaborate with the facility. In addition, sponsor should have quality agreements with the manufacturer of cell banks. |
| **9. Production** |
| 9.1. General principles |
| Lines 1136-1162 | Examples of significant changes that will need to be assessed through a comparability study could be provided. The section does not mention the need for a competent authority to approve some of these changes as they may differ from the requirements set in the approved initial clinical trial authorisation. This should be specified. Reference to existing guidelines would be appropriate. |
| 9.5. Aseptic manufacturing |
| *9.5.3. Aseptic processing validation* |
| Lines 1353-1354 | Recommend to mention the risk-based approach, as for the process simulation test as three runs are not always feasible due to batch size shortage and other constrains like complex manufacturing or unique product (reproducibility issues). Recommend to use same wording as in lines 1547-1550 and lines 1581-1586. |
| **10. Qualification and Validation** |
| 10.2. Cleaning validation |
| Lines 1547-1550 | This provides a common case in ATMP manufacturing: the same flexibility should also be included in other processes like aseptic process validation and process validation. |
| 10.3. Process validation |
| Lines 1623-1631 | Add flexibility for ATMP: concurrent validation is acceptable on a risk-based approach when a strong quality management system is in place. |
| **11. Qualified person and batch release** |
| 11.2. Qualified person |
| Lines 1661-1663 | Mention to 3rd party QPs should be included to clarify that any QP should have access to the records and/or any risk-assessment of the product for which they are taking responsibility. |
| Line 1673 | Include reference to this guidance document in conjunction with GMP requirements applied in the EU. |
| 11.3. Batch release |
| *11.3.1. Batch release process* |
| Lines 1752-1755 | Certification of finished product batch by QP after changes to the manufacturing process should be added, indicating that QP should be aware of the changes and have access to risk-assessments to evaluate the relevance of the change. |
| Line 1772 | Include reference to CMO or CRO, where this responsibility has been contracted and detailed in agreement between both parties. |
| Line 1775 | Typo: Side should be Site. |
| Line 1776 | Where site to site transfers occur, sponsor and QP approval should be included. |
| 11.5. Administration of out of specification products |
| Lines 1814-1817 | It would be advisable to provide the relevant competent authorities with a risk-assessment to evaluate the likelihood of having out of specification products (or have this as part of a document included in the application submitted) to streamline the process of notifying instances of administration of out of specification products. |
| **12. Quality control** |
| 12.2. Sampling |
| *12.2.2. Retention of samples* |
| Lines 1866-1870 | Indicate that a risk-based approach is required when retention of reference samples is not possible. |
| **14. Quality defects and product recalls** |
| 14.2. Product recalls |
| Lines 2052-2053 | Requirements of the action plan for when a product recall is not possible should be provided in the guidance. |
| **15. Environmental control measures for ATMPs containing or consisting of GMO’s** |
| Lines 2055-2073 | Reference to existing guidelines should be incorporated. A homogenous approach between different member states should be considered. |
| **16. Reconstitution of product after batch release** |
| 16.2. Obligations of the ATMP manufacturer in connection with reconstitution activities |
| Lines 2104-2105 | Involvement of QP on assessment of validated reconstitution processes should be clarified. |