**Comments on European Commission Consultation Document**

**‘Good Manufacturing Practice for Advanced Therapy Medicinal Products’**

**Issued 28-Jun-2016**

**Ref.** <http://ec.europa.eu/health/files/advtherapies/2016_06_pc/2016_06_draft_guideline.pdf>

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This document constitutes the joint EBE/EFPIA response document to the European Commission consultation on the guidance document ‘*Good Manufacturing Practice for Advanced Therapy Medicinal Products*’.

EBE (European Biopharmaceutical Entreprises) operates as a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA). EBE is the European trade association that represents 57 biopharmaceutical companies of all sizes operating in Europe.

EFPIA (the European Federation of Pharmaceutical Industries and Associations) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 42 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies.

Both trade associations are registered in the transparency register of the European Commission :

* EBE Register ID number : 768792210017-73
* EFPIA Register ID Number: 38526121292-88

**General comments**

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| EBE/EFPIA welcome this consultation and thank the Commission for preparing this second draft document following the extensive comments made on the 2015 consultation document. |
| EBE and EFPIA are in complete support of the Commission’s initiative to draw up guidelines on good manufacturing practice specific to advanced therapy medicinal products, as mandated by Article 5 of Regulation 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC. Irrespective of the final nature of the guidelines that the Commission wishes to choose (stand alone document or annex to existing GMP guidelines, see our general comments below), we firmly believe that clarity on how to apply GMP for the manufacture of all ATMPs is necessary to support the development and commercialisation of these medicinal products. |
| In particular, we are pleased to see that there is now clarity that “compliance with GMP should be ensured for all ATMPs (including investigational ATMPs), regardless of whether they are developed in a hospital, academic or industrial setting”. |
| We also appreciate and fully support the application of a risk-based approach and the flexibility offered in certain areas to accommodate the specific characteristics of ATMPs. This approach will help to provide a regulatory environment that facilitates the development, manufacture and appropriate control of quality for these complex and variable products, leading to regulatory approval and availability to patients who will benefit from them. |
| We have a number of general comments on some key areas followed by specific comments aimed at making the current draft stand alone document more complete, should the Commission decide to pursue the stand-alone approach. |
| **Standalone guidance**  During the 2015 round of consultation, our comments indicated that either more detail should be added to develop a stand alone guidance, or, alternatively, less detail and more cross-references should be included to develop an annex to the current GMP requirements for medicinal products in the EU, discussing only the specifics for Advanced Therapies. We acknowledge the work that has been done on the draft guideline on GMP for ATMPs, adding further detail from EudraLex Volume 4 into this document to help meet the Commission’s stated intent of a standalone document on GMP for ATMPs. However, having had the opportunity to consider the revised, stand alone draft, we have now come to the conclusion that the interests of all developers of Advanced Therapy Medicinal Products would be best served by **a specific ATMP Annex to EudraLex Volume 4.**  Advantages of an ATMP Annex approach would be:   * Full body of GMP requirements in one place. * No need to repeat the basics from Chapters 1 – 9. * Readily able to cross-refer to the relevant parts of other Annexes, rather than to repeat text. * Elimination of risk of discrepancies between written GMPs and significantly reduced burden of maintenance (In the past 5 years, 7 of the 9 Chapters and 5 relevant Annexes have been updated or are in process of update. The standalone document would have required revision for each of these changes.)   Whilst we accept that not all elements of GMP applicable in a traditional Pharmaceutical manufacturing environment may be applicable to small scale production of ATMPs, we suggest that the commonalities significantly outweigh the differences and that the exceptions could be readily addressed through appropriate wording in an Annex.  The following points are highlighted with regards to the current standalone document:   * It is suggested to fully align, as applicable, with the EudraLex Volume 4 Part I, II, and III chapters as well as all Annexes. (E.g., the current draft does not include all Annex 2 articles, relevant to ATMPs.) * Much of the added detail has come from Annex 1 on sterile products, which is currently being revised. It will be important to ensure that these elements are aligned with the Annex 1 revisions. It is suggested that this document is not finalised until the changes to Annex 1 proposed by the EMA/PICS team have been issued.More generally, the document should be subject to future revision at an appropriate frequency to ensure ongoing alignment with relevant core GMP expectations (EudraLex Volume 4, and new GMP guidelines for IMPs). This comment also applies to changes to other referenced legislation requirements, e.g., the definition of ‘infected donors’ in footnote 4 based on current Directive 2006/17/EC. * It is suggested that additional elements from EudraLex Volume 4, Part 1, Chapter 1, relating to the quality system should be incorporated into this document, in particular those which emphasise the role of management in assuring quality and in relation to expectations for periodic product quality reviews. * Useful additional information about the hygiene and monitoring requirements associated with different area classifications has been provided in Sections 3 and 4. However, there is a lack of guidance pointing to what grade areas are required for different types of activity. Although this should be determined by risk assessment, guidance along the lines of EudraLex Volume 4, Annex 1, paragraph 17 could be useful. * In Section 3.4, the flexibility afforded to ‘small organisations’ allowing for batch-specific definition of QC and Production staff is appreciated and valuable to some ATMP manufacturers. However, it is suggested that ‘small organisations’ should be further elaborated to constrain any undermining of the general GMP expectation for full time independence of Production and Quality Control. * A glossary of terms would be a very useful addition. Examples of terms that would be useful to define are ‘substantial’ and ‘non-substantial’ amendments to IMPD dossiers; ‘closed system’; ‘dedicated’, ‘separate’ and ‘seggregated’ in relation to facilities; ‘anatomical environment’ used in Section 6; ‘PAT’ (used in Line 1614); ‘cell recovery’ (Line 2089). In addition, including reference definitions of ‘ATMP’ and some key terms associated with ATMPs, such as ‘allogeneic’ and ‘autologous’ would be useful. * Further cross-references to other guidance would be beneficial. For example:  - ICH Q9 in relation to risk-based approach in Section 2;  - ICH Q8 in relation to control strategy;  - ICH Q5A on testing biologics in relation to potential viral contamination from human cells in Sections 7.2 (Line 960 et seq) and 7.3 (Line 1007 et seq). * In some places, reference to other EMA guidance and the European Pharmacopoeia will also be beneficial. |

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| **Request for a stakeholder meeting**  With the aim of reaching a reasoned decision on whether a stand-alone guideline on GMP for ATMPs or an Annex to the existing EudraLex Volume 4 GMP guidelines would best address the needs of all involved stakeholders (e.g., ATMP developers & manufacturers, GMP inspectors and Commission), we would very much welcome a stakeholders meeting prior to the finalisation of these guidelines. |
| **Traceability**  Whilst the document addresses this topic in section 6.6 with respect to traceability of cell/seed stock, there is very little mention regarding the need to maintain a chain of identity of the donor of cells/tissue through the ATMP manufacturing process to the finished product distribution to the recipient and vice versa. |
| **Administration of out of specification products (Section 11.5)**  We understand this section has been added to remind developers of their ethical responsibilities and the importance of working with the treating physician in regards to the circumstances of the patient, particularly in the case of autologous products. However, we have significant concerns regarding the inclusion of Section 11.5:   * Although it is conceivable for administration of an out-of-specification product to be in the best interest of the patient, there are significant legal/ethical challenges associated with allowing this possibility and, should this section be retained, it requires enhancement to cover these. * Product specifications should be set on the basis of product and process knowledge with an appropriate flexibility to account for reasonable expectations of biological variation. Consequently, a product that is out-of-specification will vary significantly from any product for which there is experience or expectation of clinical safety and efficacy. * Certification of an out-of-specification batch, or supply of a batch that has not been certified and then released, goes against the fundamental legal obligations of the manufacturing authorisation holder and their qualified person and has the potential to create significant liability issues. * Further, we have concerns that, should administration of such products lead to death, it could undermine public confidence in ATMPs and set back future developments. * **We would therefore prefer for there to be regulatory authority acceptance of wider specifications for certain parameters for certain products rather than for the administration of out-of-specification products to be allowed**. This would help to ensure regulatory oversight and safeguard manufacturers and their QPs. **As such, we consider that this is best dealt with through CMC guidance and that this section should therefore be deleted from the GMP guideline**.   Should this section be retained:   * It is suggested that it should be possible to identify up-front whether a product might be eligible for handling under this section as part of the regulatory submission. Wording can then be incorporated that would provide a basis for the QP to use as reference and thus still fulfil their legal duty. Thus, for example, an autologous gene therapy for a rare, life-threatening, condition might be identified as eligible for consideration; most allogeneic products would not. * It is suggested that competent authorities should be notified of all administrations of out-of-specification products, not just those given to clinical trial subjects. If the intent is to restrict application of this section to investigational ATMPs, then this should be stated explicitly. |
| **Environmental control of GMOs (Section 15)**  We suggest that this section is deleted and reference made to existing regulations and guidance on the control of GMOs to avoid duplication and risk of future divergence. |
| **Automated production (Section 17)**  We welcome the development of text on automated production in Section 17.  Many of the points in this section are not specific to automated production, e.g., equipment validation; procedures; maintenance; staff training, etc. It is suggested that the focus should be on those aspects which relate to the responsibilities of the manufacturers and users of the automated equipment and the potential use of the equipment in a non-GMP environment (see below).  We acknowledge the clarification provided regarding the current legal situation with application of Regulation 1394/2007 and GMP requirements where the output of an automated production system meets the definition of an ATMP in Section 17.1, Lines 2118 – 2124. This position would seem to act as a barrier to ‘in hospital’ processing, since a hospital clinical environment such as an operating theatre would not have a manufacturing authorisation, but Lines 2174 – 2181 seem to imply that such is possible. In fact, in such a setting, not the ATMP manufacturer, but the treating physician or hospital staff may be the user of the automated production system. We would appreciate further clarification on this point because, as technology develops, ‘in hospital’ processing using automated equipment may be the best option for well controlled and timely delivery of such therapies to the patients who need them. Tied with this, the potential flexibility regarding the Qualified Person in Section 17.6 is welcome, but it is not clear how this could be applied to ‘in hospital’ processing given that this is a clinical environment, not a GMP environment, and a QP is therefore unlikely to be on staff. There is also still need for further elaboration on how various requirements (e.g. medical device, ATMPs) may coexist in situations such as ‘in hospital’ processing.  With these challenges in mind we suggest further multi-stakeholder dialogue is needed to better understand this topic and how legal obligations could be adapted the various settings in which automated production may take place, in particular in an ‘in hospital’ processing environment. |
| **Next steps once the guidelines are adopted - Need for training**  **In order for all involved stakeholder to develop a consistent understanding of the GMP requirements for ATMPs, once the GMP guidelines are adopted, we would suggest that training on the guidelines and their application be held with manufacturers of investigational and commercial ATMPs, regulators and ATMP GMP inspectors. We would be pleased to offer our assistance in contribution to the curriculum development and the training, if thought appropriate.** |

**Specific text comments**

| **Section** | **Line no.** | **Comment / Rationale** | **Proposed change / suggested text** |
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| 1 | 119 | Suggest also include preventive actions | ... the implementation of appropriate corrective **and preventive** actions(s); |
| 1 | 122 | It is suggested that recall is specifically mentioned as one possible outcome | ... appropriate measures are taken. **Arrangements should be in place for the possibility of recall being required.** |
| 1 | 109 - 124 | Suggest that change management is also included within this listing | Add new bullet   * **Arrangements are in place for an effective change management system** |
| 1 | 128 - 130 | It would be useful to state explicitly here that these guidelines apply to Hospital Exemption products and that they are intended to standalone from EudraLex Volume 4 (as opposed to supplementing it). | These Guidelines ~~develops~~ **provide details of** the GMP that should be applied ~~in~~ **to** the ~~manufacturing~~ **manufacture** of advanced therapy medicinal products in the EU (including advanced therapy investigational medicinal products **and those produced under the Regulation 1394/2007 ‘Hospital Exemption’**). **They are independent of the EudraLex Volume 4 guidelines applicable to other medicinal products.** |
| 1 | 138 | Suggested wording change for greater clarity | ~~It is recalled,~~ **H**owever, ~~that~~ non-substantial amendments can be ~~introduced~~ **made to the procedures and information stated** in the investigational medicinal product dossier without the **prior** agreement of the compentent authorities. |
| 2.2 | 180 | Suggest adding some wording regarding risks related to vector characteristics. | .., the biological characteristics of the vectors (**e.g., replication competence or reverse transcription**), the level… |
| 2.2 | 183 | Suggest to add stability testing as also applies. | …, including in-process testing, and batch release testing **and stability testing**, should be… |
| 2.2 | 197 | It is suggested that the importance of ensuring adequate management and transition of knowledge throughout development is specifically called out given that currently a lot of early ATMP development is occurring in academic institutions and is then transferred to a manufacturer. | Add to existing text  **The knowledge gained throughout the product lifecycle should be well managed. Where there are transitions in responsibility, e.g., from an early developer to a manufacturer, it is important that there is a transfer of accummulated knowledge.** |
| 2.2 | 206-208 | Suggest that the term ‘quality strategy of the manufacturer when the risk-based approach is applied’ needs exemplifying to aid understanding | Add a sentence:  … should also describe, as appropriate, the quality strategy of the manufacturer when the risk-based approach is applied. **For example, the manufacturer’s approach to assuring sterility of the product; in process testing strategies for assuring product quality; other process-specific controls implemented to mitígate identified risks.** For aspects that… |
| 2.3.2 | 248 – 250 | Suggested wording for greater clarity | In these cases, **a risk-based approach should be used to design** an ~~adequate~~ **appropriate** control strategy ~~should be designed~~ **based on current knowledge and experience of the manufacturing process and in-process controls** (and, as appropriate, ~~be explained~~ **justify this** in the marketing authorisation/clinical trials authorisation application) ~~based on the validation of the manufacturing process and the in-process controls~~. |
| 2.3.2 | 252 - 254 | Suggest adding text around real time testing for release of time sensitive materials and the results need to be relevant to the critical quality attributes of the finished product | Added text proposed:   * Testing of intermediates (instead of the finished product) or in-process controls (instead of batch release testing) **or real time testing can be particularly useful to support decisions to release short shelf-life products for administration** if the relevance of the results from these tests to the **critical quality attributes of the** finished product can be demonstrated |
| 2.3.2 | 268-272 | It is suggested to extend the text on visible particulate matter. Often, a combination of measures need to be taken to assure the final product does not contain foreign visible matter and there is also batch-to-batch consistency from a particulate point of view. In addition, cells may form clumps in the sub-visible and/or visible particulate matter range and those may potentially be a safety concern (e.g., when administered into the eye). Hence, a risk-based approach should be taken to assess which in-process and/or fnal product measures are put in place to assure a consistent and safe product is administered. | As cells in suspension are not clear solutions, it ~~is~~ **may be** acceptable to limit the particulate matter test to foreign visible particles, provided that alternative measures are put in place**,** such as controls ~~of input~~ of particles from **input** materials and equipment used during manufacturing **(e.g., filtration of raw material solutions**), **and**/or the verification...(without cells), **and environment control (see section 4.2.3).** **Characterisation data providing understanding of the particulate properties of the process (e.g., through fluid path simulation) and ATMP, including the indication/route of administration (e.g., for intra-occular administration, cell clumps in the sub-visible or visible particulate range may have implications for quality, safety or efficacy), need to be accounted for when defining the appropriate particulate matter tests and risk assessment should be used to justify appropriate control measures.** |
| 2.3.2 | 273 / 274 | It shouldalso be possible to waive on-going stability in the case of very limited material, e.g., for autologous therapies where the entire quantity of each batch is dosed back to the patient. As with the previous examples, provisos should be given. | It may be justified to waive the on-going stability program for products with a very short shelf life **or where there is insufficient material to perform the study, based on development/validation data** |
| 2.3.3 | 284 – 292 | This paragraph is very confusing and we are not clear what it is intended to say.. | Needs rewording. |
| 2.3.3 | 295-302 | Suggest that there should be reference to Section 4.2.2 here and that the wording is simplified since it seems to be saying that all manipulations must be performed in Grade A, though there can be relaxation of the background classification, subject to risk assessment. | Suggest rewording:  …substantial manipulation. **The environmental classification of manufacturing areas should be based on risk assessment with reference to the expectations in Section 4.2.2. All manipulations of product should be performed in a Grade A environment. Any relaxation to the background environment classification for open systems should be supported by a risk assessment with** ~~When manufacturing operations take place in an open environment in premises other than a critical room of grade A in a background clean area of grade B, a risk-analysis study should be conducted (~~particular consideration ~~should be~~ paid to the time that the product is exposed to the environment~~)~~ and ~~it should be demonstrated~~ **demonstration** that the implemented control measures are adequate to ensure aseptic manufacturing. Under no circumstances it is acceptable to conduct manufacturing operations ~~in premises with air quality classification lower than a critical clean room of grade A in~~ **with** a background ~~clean area of~~ **air classification lower than** grade D. |
| 2.3.3 | 311 | QPs certify medicinal products rather than releasing them. | Correct wording:  QP ~~release~~ **certification** is an essential requirement… |
| 2.3.4 | 320/321 | Suggest that these examples may be acceptable, subject to risk assessment, rather than that they are acceptable. | The following are examples of the additional flexibilities that ~~are~~ **may be** aceptable**, subject to risk assessment,** in the case of investigational ATMPs |
| 2.3.4 | 322-327 | Suggest that these expectations should be aligned with those in Section 2.3.3 for ATMPs not subject to substantial manipulation. Also, that risk assessment is applicable for all IATMPs, not just for first-in-man studies. | **The environmental classification of manufacturing areas should be based on risk assessment with reference to the expectations in Section 4.2.2. All manipulations of product should be performed in a Grade A environment. Any relaxation to the background environment classification for open systems should be supported by a risk assessment, with particular consideration of** ~~For first-in-man clinical trials, production in an open environment may be performed in a critical clean area of grade A in a background clean area of grade C if~~ appropriate controls of microbiological contamination~~, separation of processing procedures~~, and validated cleaning and disinfection**, to demonstrate** ~~are put in place. A risk-analysis study should be conducted and it should be demonstrated~~ that the implemented control measures are adequate to ensure aseptic manufacturing. |
| 2.3.4 | 328-331 | It should be clarified whether the statement about manufacturing activity being ‘very low’ relates to the facility or to individual products. The proposed amended wording on the right is based on an interpretation that this is about the facility. | Add wording to clarify:  …when the manufacturing activity **in a facility** is very low, … |
| 3.3 | 379 | This should include moustache covering also | Hair and, where relevant beard **and moustache** should be covered. |
| 3.3 | 417-418 | The risk to personnel resides not just with the product but with some of the materials used in production. As some personnel handle the materials but not the products, it is important to highlight both risks. | Add to the end of the last sentence in the paragraph, ‘ **and the materials used in its production**.’ |
| 3.4 | 430-432 | Text here is confusing. Consider suggested text. | Proposed amended text:  In small organisations, where teams are multi-skilled and trained in both QC and production activities, it is acceptable that **a person is responsable for one of these roles (production or quality control) for a given batch, and for the other role for a subsequent batch. At no time is it aceptable for a person to perform both roles for a single batch.** ~~the same person is responsible for both roles (production and quality control) with respect to different batches.~~ |
| 4.2 | 468/469 | Suggest additional wording to make it clear that this is not an exhaustive list of manufacturing activities requiring segregated areas. | Proposed amended text:  Segregated production areas (*see* Section 9.4(i)) should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. ~~Specifically~~, **Examples of** manufacturing activities **that should be undertaken in segregated areas would include those** involving infectious viral vectors (*e.g.* oncolytic viruses) or materials from infected donors4 ~~should be done in a segregated area~~. |
| 4.2 | 469 / Footnote 4 | Via footnote 4, reference is made to current donor testing requirements. However, these requirements may change in the future (e.g., addition of Zika virus testing). It will therefore be important for appropriate trigger mechanisms to be in place to revise this guidance document in the event that this happens. |  |
| 4.2 | 472-474 | Suggest add wording to this sentence to help explain why it is here. | Proposed added text:  … before any subsequent manufacturing in the same area can occur **(segregation in time)** |
| 4.2.1 | 461-462 | As ATMPs include a wide range of products the request for a dedicated manufacturing area should be based on the risks of a specific product, not on a formal classification of ATMPs/non-ATMPs. | Proposed change of this sentence: **In a multi-product facility, based on a risk assessment a dedicated area may be needed** **to manufacture a specific authorised ATMP**. |
| 4.2.1 | 487 - 490 | Air change rates should also be considered as part of the design of the facility and it is suggested that this is stated explicitly within this paragraph or the preceding one. | Additional sentence following current text, Line 490:  **Appropriate air change rates should be part of the design and qualification.** |
| 4.2.2 | 520 | It may be possible to justify preparation of solutions which are to be sterile filtered in an environment less than grade C. | Proposed addition:  Preparation of solutions which are to be sterile filtered during the process can be done in a grade C environment. **Subject to risk assessment and appropriate controls, a less controlled environment may be justified for this activity.** |
| 4.2.2 | 533 | Where disinfectants are used, the cleaning regimen should also ensure that residual cleaning agents/disinfectant are sufficiently removed to minimize product contamination | Proposed addition:  Appropriate cleaning/sanitation of clean areas**, including the removal of residual cleaning agents/disinfectants,** is essential |
| 4.2.3 | 542 | It is not clear what is meant by “airflow direction” for the Environmental Monitoring program. Suggest this is only relevant as an environmental monitoring parameter where unidirectional airflow is required. | Add text:  ... airflow directions **(where unidirectional airflow is required)**, temperature... |
| 4.2.3 | 570/571 | As currently worded, although using the word ‘may’, the text could be read as an HVAC interruption typically triggering qualification. It is suggested that wording is changed to require an assessment of HVAC system interruption to determine whether any further action is required. | While at rest, the HVAC system should not be interrupted~~, as this may trigger the need for re-qualification~~. **In the event of an interruption, a risk assessment should be conducted to determine any actions that may be required, e.g. additional monitoring, taking account of the activities performed in affected areas, whether these are open or closed, etc.** |
| 4.2.3 | 574 | ‘spraying of disinfectants’ is not a good example of ‘intrinsic particle generation by the process’ in a closed system and it is suggested that this be deleted | … by the process *~~(e.g.~~* ~~spraying of disinfectants).~~ |
| 4.2.3 | c. 600 | The media used for viable monitoring and times/temperatures for incubation post sampling should be justified and specified in procedures. This should be stated explicitly (new sentence) | Add sentence:  **The media used and times/temperatures for incubation post sampling should be justified and specified in procedures**. |
| 4.2.3 | 601 | In keeping with current GMP regulatory agency expectations, it is suggested that ‘average values’ is deleted and that the ‘<1’ figures in the table are changed to ‘0’ for Grade A. | apply ~~(average values)~~: |
| 4.3 | 630 | If special storage conditions are required, then as well as specifying them and monitoring, validation should be performed to demonstrate capability. | ... specified, **validated** and monitored. |
| 5.1 | 656-658 | The section is discussing equipment but this paragraph is about components. Is this relevant here? If so it needs to be clarified what is meant by components (parts of the equipment as opposed to process items/primary container closure). |  |
| 5.2 | 678 - 680 | Whilst decontamination (sterilisation) procedures should be validated, cleaning procedures for investigational ATMPs might be assured by verification rather than validation (as recognised in Section 10.2). | ... should **by first intent** be validated, **but cleaning verification is acceptable for early batches of investigational ATMPs** (see Section 10.2) |
| 5.2 | 683-684 | This sentence should be expanded to add a requirement to ensure the required environmental standard has been re-established prior to restarting manufacture. | When repair or cleaning operations occur in a clean area, production should not be restarted until it has been verified that the area has been adequately cleaned **and the required environmental standard has been re-established**. |
| 6.2 | 768 to 776 | Specification acceptance criteria for stability studies might differ from the release specifications and this possibility should be allowed for in the list | Add new bullet:  **-acceptance criteria for stability if different from the release specification** |
| 6.2 | 786-799 | The information listed here as being required for the Product Specification File is incomplete when compared with the text in the draft **Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use** | Either align the requirements in this section with the ‘Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use’, or simply refer to this document rather than providing details here. |
| 6.3 | 809-840 |  | Significant items that are missing include:   * Line clearance checks * Maintenance and calibration records for critical equipment * Training records for staff * Change control records |
| 6.3 | 833 | Reconciliation of materials can be more important than yield and it is suggested that this is included. | the product yield **and materials reconciliation** obtained at relevant stages of manufacture; |
| 6.5 | 868/870 | It would be preferable for IATMP batch documentation to be kept for a defined period of time from the date of manufacture rather than trying to tie this to trial completion or discontinuation dates. This enables batch documentation to be archived promptly and for the retention period to be set at the time of archive rather than being dependent on a future event. It is accepted that taking this approach will require a period longer than five years to be set. | For investigational ~~medicinal products~~ **ATMPs**, the batch documentation must be kept for at least **fifteen years from the date of manufacture** ~~five years after the completion or formal discontinuation of the last clinical trial in which the batch was used~~. |
| 6.6 | 881-884 | It is critical to be able to track the cells used in production, back from any point to the donor information, for timely investigations of suspected transmission of disease by the product. It is misleading to make the statements, ‘so that the donor can be identified’. This has the potential to have donor information, such as name or date of birth etc, being shared beyond the collections sites. | Proposed rewrite of this sentence:  **A system which enables the bidirectional tracking (traceability) of cells/tissue (and the relevant donor information) contained in ATMPs from the point of donation, through production, to the delivery of the finished product to the recipient should be created. The system can be manual or electronic.**  ~~The traceability of the cells/tissues contained in ATMPs should be ensured so that the donor of the cells and tissues used as starting materials can be identified, through the entire manufacturing process, storage and transport, up to the delivery of the finished product to the recipient~~. |
| 6.6 | 906-907 | In addition, for biological materials it is important to describe the country of origin, species, and make a reference to an EDQM certificate, if applicable. | For biological materials, the identification of the supplier ~~and~~**,** the anatomical environment from which materials originate, **the species and the country of origin** should also be described**. In addition, where applicable, reference should be made to an EDQM certificate.** |
| 7.1 | 916-929 | A section on the benefits/need to qualify suppliers should be added to this section in line with industry best practice | Suggest adding text in this section based on EudraLex Volume 4, 5.27, enabling some reduction in repetition in sections 7.2 and 7.3:  **The selection, qualification, approval and maintenance of suppliers of raw and starting materials, together with their purchase and acceptance, should be documented as part of the quality system. The level of supplier supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity, phase of development and the final use to which the material is put. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.** |
| 7.2 | 931 - 933 | Suggest adding in text after the current first sentence that recognises the fact that not all raw materials used in the manufacture of ATMPs may be well characterised and that the focus should be on attributes important to product safety and performance. | Raw materials should be of suitable quality having regard to the intended use. **For poorly defined or undefined materials or solutions (e.g,. cell culture medium) the attributes important to ensure safety and performance should be monitored and controlled throughout the product development life-cycle.** |
| 7.2 | 942 | Suggest adding ‘safety tests’ to the example as these are critical and are not always performed by the supplier. | …by means of testing (e.g., functional test**, safety tests**). |
| 7.2 | 952-959 | It is suggested that this section requires strengthening in relation to identity testing.  Clarification is also suggested in relation to raw materials authorised as medicinal products - not only are certificates of analysis not required, but also the level of supervision may also be reduced. | … Reliance on the certificate of analysis of the supplier ~~is~~ **may be** acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers **with periodic independent verification of test data**). **Identity testing following receipt should be performed unless justifed otherwise.** For raw materials that are authorised as medicinal products (*e.g.* cytokines, human serum albumin, recombinant proteins) the certificate of analysis of the supplier is not required **and the level of supervision may be reduced**. |
| 7.2 | 961 | It is suggested that mycoplasma are worth highlighting specifically within this sentence | ...emphasis on viral, **mycoplasma** and microbial safety... |
| 7.3 | 980 | It is suggested that this section should have some text specific to autologous cells which are starting materials for some ATMPs. A suggestion is provide. | Suggested additional text:  **Autologous cells: The roles and responsibilities of both the clinical and manufacturing sites need to be well defined. Controls over activities undertaken at clinical sites, e.g., cell preparation and freezing prior to transport, should be agreed together with the specifications for acceptance by the manufacturer. Specifications need to be defined according to both the patient characteristics (including limitations) and the process capability, taking into account the flexibility that may be required across the patient population.** |
| 7.3 | 990 | It is suggestd to add storage as this is an important step. | ..., testing and control, **storage**, and other aspects... |
| 7.3 | 997-999 | Blood and tissue establishments: Although audits are not required, the authorisation should be verified and quality agreements should be in place. It is suggested that this is explicitly stated. | Blood establishments and tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23 do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing**, but the authorisation should be verified and a quality agreement put in place**. |
| 8 | 1071/ 1072 | It is suggested that the wording is strengthened to say that master and working seed lots/cell banks should be used for allogeniec products where single donor material is to be used for large number of of patients. | ... between the donor and the patient**, especially where single donor material is to be used for a large number of patients.** |
| 8 | 1097-1100 | The section should be expanded to make this more generic and introduce the need for continuous monitoring where relevant | Suggested rewording:  Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be ~~recorded~~ continuously **monitored** and **records retained. Depending on criticality, remote alarm systems with a staff call out process may be necessary.** ~~, where used, the liquid nitrogen level monitored.~~ Deviation from set limits and corrective and preventive action taken should be recorded. **Other parameters necessary to ensure safe storage may also require monitoring. For example, where used, liquid nitrogen levels should be monitored.** |
| 8 | 1127 - 1129 | Should include the expectation that history and traceability of cell stocks/banks as far back as possible should be performed whether GMP or non-GMP. | Propose addition:  In all cases, **the history and traceability of cell stocks/banks should be established as far back as possible and** the overall responsibility for the quality – as well as the impact thereof on the safety and efficacy profile of the product- lies with the ATMP manufacturer. |
| 9.1 | 1159 - 1162 | Prior to a deviation being approved, it should be investigated to establish potential impact. | If a deviation occurs, **its impact should be assessed in accordance with a quality risk management process and documented with approval** ~~it should be approved in writing~~ by the person responsible for manufacturing, ~~with the involvement of~~ **and** the person/department responsible for quality control ~~when appropriate~~. **Batch(es) concerned should only be progressed for use if it can be concluded that the potential impact on quality, safety and efficacy is negligible.**  **Investigations should attempt to identify the root cause(s) of the deviation and any appropriate corrective or preventive actions should be implemented.** |
| 9.2 | 1172 | Identity testing of incoming materials should be the norm and it should be clear that other testing may be required as part of the appropriate measures put in place to mitigate risks | ~~Where necessary, identity testing should be considered.~~ **Identity testing should be carried out unless otherwise justified. Other testing may be required to appropriately mitigate risks.** |
| 9.2 | 1186/ 1187 | Some words missing from this sentence | The compatibility of labels with **storage or processing conditions** (e.g. ultra-low storage temperatures, waterbath) should be verified. |
| 9.3.1 | 1193-1202 | Reference to the EMA guidance documents and European Pharmacopoeia in relation to the ‘appropriate quality’ of water, including the need for thhe system to be appropriately designed and qualified to avoid microbial contamination. | Add footnote with references |
| 9.3 | 1206 | Filters used should be subject to integrity testing | ... passed through micro-organism retentive filters. **Filters should be subject to integrity testing.** |
| 9.3.3 | 1208-1210 | Reference to the relevant pharmacopoeial sections (testing to WFI standards) should be made in this section. | Add footnote with reference |
| 9.4 |  | The cross-contamination risk associated with personnel flow in multi-product facilities should also be highlighted in this section with appropriate controls to mitigate. | Suggested additional text to add into this section:  **The cross-contamination risks associated with personnel in multi-product facilities should be assessed and mitigated. Staff should not be able to move directly between production areas being used for different products, but required to pass through appropriate clothing changes.** |
| 9.4 | 1246 | It should be possible for cleaning to be verified in lieu of validation | ...procedures should be validated **or verified** (see Section 10.2) |
| 9.5.1 | 1260- | It is suggested to include here some wording around the application of the RBA to assess the need for controls to reduce the risk of (cross) contamination throughout the manufacturinig process | Add to section 9.5.1 ‘General Principles’ –  **The application of the risk based approach should be used to determine the controls necessary to reduce the risk of microbial contamination and cross contamination for all production steps starting with cell separation/isolation through to filling into final product container. The measures implemented should be verified as effective.** |
| 9.5.1 | 1267 - 1289 | This section is confusing. In 1267/1268, closed systems are stated to be different areas, which may be present within the same room. But in 1283/1284 and 1288/1289, the word ‘area’ is used when ’room’ would appear to be intended.  It is suggested that it is not appropriate to conduct concurrent production of any products in the same ‘area’ and that paragraph 1283 – 1289 is deleted.  In addition:   * There need to be appropriate controls to prevent cross-contamination or mix up of materials within the room prior to entering or after being removed from isolators. * Added wording is suggested in 1271 – 1274 to clarify incubator/isolator in this sentence | Delete paragraph 1283 – 1289.  Modify paragraph 1267 – 1274 as follows:  Separation in place: **Concurrent production in the same area is not acceptable. However,** “closed systems” may be used to separate activities within the same room (each closed system is to be regarded as an area). Thus, the use of more than one isolator (or other closed system) in the same room at the same time is acceptable, provided that there is separate~~d~~ expulsion of the exhausted air from the isolators and regular integrity check of the isolator**s together with appropriate mitigation measures to avoid cross-contamination or mix-up of materials (e.g., closed, separate and unidirectional waste handling).** Likewise, it is acceptable to conduct a manufacturing activity in **an isolator in** a clean room which hosts an incubator which is used for a different batch/product if ~~there is separated expulsion of~~ **the** exhausted air from the isolator **is not drawn into the incubator** and regular integrity checks of the isolator **are carried out**. |
| 9.5.1 | 1292 | Verification of cleaning should be acceptable | ... a cleaning process of validated **or verified** effectiveness. |
| 9.5.1 | 1301 – 1304 | As currently written, this paragraph does not make sense as it is about when sterilisation is not possible, but it goes on to give sterile filtration of raw materials as a possible control process. | When **heat** sterilisation of articles... |
| 9.5.2 | 1318 | This section is headed ‘Sterilisation’, so the wording should focus on removal (reduction implies sanitisation) | ...in terms of removing~~/reducing~~ the contaminants... |
| 9.5.2 | 1324 | Although it is not always possible, it is suggested that wording is included regarding the additional sterility assurance that may be achieved by double filtration. | Add new sentences to end of current text in Line 1324:  **For additional sterility assurance, the possibility of double filtration should be assessed and decision taken justified.** |
| 9.5.2 | 1326 - 1328 | Use of the word ‘verified’ could be taken to imply testing which is not without risks and may not always be appropriate or necessary. We suggest use of the word ‘assured’, which would allow for the possibility of pre-use filter integrity to be achieved through a programme of supplier assurance, for example. | The integrity of the sterilised filter should be ~~verified~~ **assured** before… |
| 9.5.3 | c. 1345 | The number of units to be filled during each media fill run should be defined in the protocol or procedure. This should be stated in a new sentence, which it is suggested can follow on Line 1345 | New sentence added to existing text ending on line 1345:  **The number of units to be filled during each media fill run should be defined in a protocol or procedure.** |
| 9.5.3 | c. 1345 | There is nothing currently within the text of this section on process simulations that points to covering potential process interventions. | Suggest new sentence required between 1345 and 1346:  **The process simulations should also be used to assess potential manufacturing interventions.** |
| 9.5.3 | 1346/ 1347 | The orientation of containers and assurance that media touches all container surfaces is also important and it is suggested that this is highlighted here. | ~~After the final product container is filled, it~~ **Filled containers** should be **inverted to ensure the media touches all parts of the container/closure and** incubated for the time and under the temperature specified in the protocol/media fill procedure. |
| 9.5.3 | 1354; 1356 | It is unclear what is intended by ‘per shift’. Most ATMPs are not manufactured on a shift basis. If this is intended to address the fact that media fills should be used to qualify operatives as well as the process, then this should be stated more clearly. | 1354:  … satisfactory simulation tests ~~per shift.~~ **for the production process. All staff who may be involved in production should also be qualified by the media fill programme.** |
| 9.5.3 | 1355 - 1364 | Applying the standard frequency of process simulations for parenteral medicinal products to ATMPs is not sound reasoning. The risk associated with filling a single or small number of containers with an ATMP for an individual patient is quite different to that of filling thousands of doses of a medicinal product.  The principle of using process simulations to ensure the environment, people and process continue to work together to keep sterility assurance high is the same, but there should be more flexibility to set the frequency of simulation tests according to risk assessment. | Rewrite this section to be less stipulative regarding frequencies.  **Process simulation tests should be repeated periodically to provide ongoing assurance of both the process and production staff. The need for process simulations to be conducted in support of significant process or facility changes should also be assessed.**  **The frequency of periodic process simulation testing should be determined by risk assessment. The six monthly frequency expected for aseptically manufactured medicinal products is suggested as a benchmark against which any reduced frequency should be justified. For infrequent manufacture, process simulation tests might be scheduled ahead of batch manufacture. Three consecutive runs should be performed for each requalification unless otherwise justified through a documented risk assessment.**  ~~It is generally expected that the process simulation test with media fill test is run every six months per shift, as well as when there is any significant change to the process~~ *~~(e.g~~*~~. modification of HVAC system, equipment,~~ *~~etc~~*~~). A reduced frequency in cases of infrequent production may be justified. Thus, if the interval between the production of two batches is more than six months the process simulation test can be done just before the manufacturing of the second batch (three consecutive runs should be performed).~~  ~~When considering the frequency of the simulation test, the manufacturer is required to consider also the relevance of the media fill test for the training of operators and their ability to operate in an aseptic environment. A reduced frequency is not acceptable when the product should be administered to the patient prior to having the results of the sterility tests.~~ |
| 9.6 | 1377-1378 | The re-use of matrixes should also be supported by appropriate validation data. | Suggest adding text:  ... is discouraged. **Any such re-usage should be supported by appropriate validation data.** Acceptance criteria, operating conditions... |
| 9.7 | 1396 | Suggest that extractables and leachables testing is specifically mentioned. | Suggest adding the following sentence after ‘For authorised ATMPs, the closure procedures should be validated.’:  **Container/closure systems should be assessed for extractables and leachables.** |
| 9.7 | 1404 | An important way to help avoid mix up is to perform reconciliation of labels and materials and it is suggested that this is explicitly stated. | ... risk of contamination. **Product, labels and other packaging materials should be reconciled.** |
| 9.9 | 1412 – 1415 | The statement ‘removed from the production environment’ is unnecessary given the preceding requirement to store separately in restricted areas. | Propose instead:  ..should either be returned to the suppliers or~~, removed from the production environment~~ **sent for appropriate destruction.** |
| 9.9 | 1426 | Suggest replace ‘clinical use’ with ‘distribution or administration’ since use of the term ‘clinical use’ might be interpreted as being specific to investigational products in clinical trials whilst this sentence is applicable to all ATMPs. | ... so that they are not available for further **distribution or administration** ~~clinical use.~~ |
| 10.1.1 | 1431-1448 | The qualification of sterilisers should also be highlighted alongside the current examples due to criticality. | Add bullet:   * **Sterilisation equipment should be qualified and periodically requalified in accordance with current standards and best practices** |
| 10.1.1 | 1449 - 1456 | We suggest that this guidance should not use the wording ‘it can be assumed’ (Line 1453) and that the focus should be on ensuring a risk assessment is associated with all changes made. | Before starting the manufacturing of a new type of ATMP in premises that have already been qualified, the manufacturer should assess if there is a need for re-qualification having regard to the specific risks and characteristics of the new manufacturing process/new product. For example, if the premises have been qualified for open processing and a closed system is introduced, it ~~can be assumed~~ **may be assessed** that the (existing) qualification of the premises covers a worst case scenario and therefore no re-qualification is needed. In contrast, when the premises have been qualified for a simple manufacturing process and a more complex process is introduced that *e.g.* may require an additional level of containment, requalification is **likely to be** required. |
| 10.1.1 | 1458 – 1461 | Suggest the text about requalification (which is specific to air classification of clean rooms, not the general periodic re-evaluation of the qualification status of facilities and equipment) is incorporated into the bullet of lines 1438/1439 | Revised Lines 1438/1439:  ... and re-qualified at appropriate intervals in accordance with ISO 14644-2. **In general, Grade A areas should be requalified every 6 months with Grade B, C and D areas requalified annually. Different frequencies may, however, be justified in cases of infrequent production.**  Delete Line 1458 from ‘Requalification’ through to end Line 1461. |
| 10.1.2 (b)(i) | 1476 | In addition to instruments being appropriately calibrated, any associated alarms should be confirmed to be in place | instruments are appropriately calibrated **with any associated alarms in place**, and |
| 10.1.2 (b) | 1491 | Suggest ‘may’ be performed at vendor site, not ‘should’ | ...some tests ~~should~~ **may** be performed at the vendor’s site... |
| 10.2 | 1512 | Suggest enhancing this text to include decontamination as well as cleaning | Factors that influence the effectiveness of the cleaning **and decontamination** process**es** (*e.g.* operators, **disinfectant exposure times,** rinsing times, cleaning equipment and cleaning agents used) should be identified |
| 10.2 (ii) | 1530-1534 | The section should also mention that sampling (swabbing) should be at locations identified as “worst case”. | (ii) *Sampling procedures*: Sampling may be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. **For swabs, sampling should be from locations identified as ‘worst case’.** Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used. |
| 10.2 | 1547 / 1548 | The use of cleaning verification for IATMPs should not be restricted to volumes of production less than three batches. | For investigational ATMPs, cleaning verification is acceptable ~~when the volume of production is small (less than three batches)~~. |
| (10.3) |  | General comment: Whilst the technical transfer of testing methods is specifically addressed in 12.3, there is no text currently regarding the technical transfer of manufacture. It is suggested that this is addressed as part of the section on process validation, or in a separate new section. |  |
| 10.3 | 1567 | The term ‘validation method’ is not clear and rewording is suggested. | Suggest:   * List of analytical methods and **how they are to be validated** ~~validation method~~, as appropriate |
| 10.3 | 1615 | The statement “This does not preclude the qualification of individual steps” creates a lack of clarity with regards to expectations. Given that the preceding sentence allows for process validation to be replaced by continuous monitoring, it is suggested that this sentence is deleted. It is implicit that there is no issue with companies going above and beyond the stated requirements. Alternatively, it should be enhanced to provide guidance as to when the qualification of individual steps might be necessary. | Either delete this sentence:  ~~This does not preclude the qualification of individual steps~~.  Or, enhance it:  **Assessment of critical process parameters and critical quality attributes may still result in a decision to** ~~This does not preclude the qualification of~~ **qualify** individual steps**, where posible, for added assurance**. |
| 10.3 | 1616 – 1618 | Retrospective validation is mentioned here, which is clearly not acceptable in any other context and we don’t see that it is necessary for ATMPs either. There is no reason why ATMP processes should not be validated prospectively or concurrently using data from future batches. | Delete this section of text:  ~~Retrospective validation where time to manufacture, batch size, or other factors make prospective validation unethical~~ *~~(e.g.~~* ~~performing a biopsy only for validation purposes) or disproportionate having regard to the anticipated benefits for patients~~. |
| 10.3 | 1619-1622 | Suggest rewording this section  Firstly, autologous T-cell based ATMPs are an example, not the only possibility for applying this.  Secondly, it is suggested that the criteria should be ‘no significant differences’ rather than ‘the same’. | Suggested rewording:  Process validation for a class of products: where the same manufacturing process is used for a class of products (~~i.e~~. **e.g.,** autologous T-cell based ATMPs), the validation of the process does not need to be repeated for each of the products, in so far as the manufacturing process ~~remains the same~~ **has been assessed and no significant differences noted**. |
| 10.4 | 1637/38 | Suggest enhanced wording to point to how the suitability might be demonstrated to be fit for purpose | The suitability of analytical methods should be demonstrated for phase II and III clinical trials **(e.g.,**  **through qualification or taking account controls in place as part of the assay method),** but a full validation report is not required |
| 10.4 | 1637-1638 & 1639-1640 | The difference intended for potency assays vs all other analytical methods (other than safety and microbial assays addressed by Line 1636) is not clear and the i.e wording adds confusion rather than clarity (‘throughout clinical development’ is not ‘typically ... before phase III’, but implies from Phase I onwards).  It is suggested that Lines 1639 and 1640 are deleted and that potency assays should be demonstrated as being suitable but do not require formal validation, per Lines 1637/1638.  If the expectation is that there should be a full validation report for such assays, then this should be stated explicitly and clarity is required as to expectations relating to clinical trial phase. | Delete lines 1639/1640:  ~~Potency assays should be validated throughout clinical development (~~*~~i.e.~~* ~~typically validation finalized before phase III clinical trials)~~.  Alternatively, if expectations for potency assays are more formal than demonstration of suitability, then this needs to be clarified, e.g.:  **However, potency assays should be formally validated before Phase III clinical trials** **are started, unless otherwise justified.** |
| 10.4 | 1644 | Although pharmacopoeial analytical procedures do not require validation, they typically require product-specific qualificatgion e.g. specificity in the presence of sample matrix or demonstration of sensitivity if used for an impurity. | ... are normally considered as validated. **However they should be qualified for their intended use for each specific product or platform.** |
| 10 |  | It is suggested that there should be a new sub-section on the qualification/verification of transportation | **Verification of transportation**  **ATMPs and associated materials should be transported under conditions that assure their ongoing stability and suitability for use. Verification of transportation may be challenging due to the variable factors involved. A risk assessment should be performed to establish critical conditions and to evaluate transportation routes. Seasonal and other variations should also be considered during verification of transport. Critical environmental conditions should be continuously controlled or monitored, unless otherwise justified.** |
| 11.2 | 1674-1683 | This wording is unclear: As currently worded, it seems to imply a need for active substance testing, as opposed to the qualitative and quantitative analysis of the active substances within the product.  Further, we suggest that in the majority of cases it will be justified for ATMPs not to undergo further testing on import and that assurance of the testing is through quality oversight, not through a re-testing strategy. | Suggest rewording for greater clarity:  In case of imports of authorised ATMPs from third countries, the QP should ensure that the quality of the batch is in accordance with the terms of the marketing authorisation, including **(if stipulated)** ~~by means of~~ a full qualitative and quantitative analysis of the active substance(s) **within the product** as well as any other necessary checks.25 ~~However, it is acknowledged that for ATMPs it is not always possible to separate the testing of the active substance from the testing of the finished product~~. ~~Additionally, it~~ **It** may be justified to rely on testing performed in the third country in cases where the limited amount of material available (*e.g.* autologous products) or the short shelf-life impedes double release testing. In such cases, the testing in the third country should be conducted under conditions equivalent to those applicable in the EU **and subject to quality oversight**~~. The re-testing strategy should be~~ in accordance with the terms of the marketing authorisation. |
| 11.3.1 | 1717ff | Suggest that material traceability should be explicit in this list of checks that need to be carried out | Add bullet into the list:   * **The traceability of materials used, in particular assurance that autologous or 1:1 donated materials are correct for the intended patient** |
| 11.3.1 | 1761 – 1763 | The retention period of the register of QP certification for IATMPs should be decoupled from the clinical trial duration. We accept that this will require a longer retention period to be applied. | For investigational ATMPs, the certification must be kept for at least ~~five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longest~~ **fifteen years from date of certification.** |
| 11.3.2 | 1782 – 1785 | Suggest it should be made clear that the minimum available analytical results allowing certification for administration should be specified. | ... the available analytical results **(minimum testing requirements as defined in site processes/procedures)** for review... |
| 11.5 | 1808 – 1817 | Although it is conceivable for administration of an out-of-specification product to be in the best interest of the patient, there are significant legal/ethical challenges associated with allowing this possibility and, should this section be retained, it requires enhancement to cover these.  Product specifications should be set on the basis of product and process knowledge with an appropriate flexibility to account for reasonable expectations of biological variation. Consequently, a product that is out-of-specification will vary significantly from any product for which there is experience or expectation of clinical safety and efficacy.  Certification of an out-of-specification batch, or supply of a batch that has not been certified and then released, goes against the fundamental legal obligations of the manufacturing authorisation holder and their qualified person and has the potential to create significant liability issues.  Further, we have concerns that, should administration of such products lead to death, it could undermine public confidence in ATMPs and set back future developments.  We would therefore prefer for there to be regulatory authority acceptance of wider specifications for certain parameters for certain products rather than for the administration of out-of-specification products to be allowed. This would help to ensure regulatory oversight and safeguard manufacturers and their QPs.  As such, we consider that this is best dealt with through CMC guidance and that this section should therefore be deleted from the GMP guideline.  Should this section be retained, it is suggested that it should be possible to identify up-front whether a product might be eligible for handling under this section as part of the regulatory submission. Wording can then be incorporated that would provide a basis for the QP to use as reference and thus still fulfil their legal duty. Thus, for example, an autologous gene therapy for a rare, life-threatening, condition might be identified as eligible for consideration; most allogeneic products would not.  It is suggested that competent authorities should be notified of all administrations of out-of-specification products, not just those given to clinical trial subjects. If the intent is to restrict application of this section to investigational ATMPs, then this should be stated explicitly. | We suggest that this section is deleted. Instead, the fundamental for a product to meet its specification should be retained and those scenarios for which this section is intended to be a solution should be dealt with through CMC guidance and appropriate flexibility in CTA/MAA product specifications.  In the event that this section is retained, we suggest the following:  In cases where, for imperative reasons linked to the health of the patient, an out of specification product **may** need~~s~~ to be administered to the patient, **this should be anticipated in the regulatory filing and statement made regarding which specification parameters might be deviated from, subject to risk assessment and agreement of the treating physician.**  **On the occurrence of such a situation,** the manufacturer should provide the treating physician with its evaluation of the risks (the possibility of reprocessing may be considered as appropriate). The agreement of the treating physician to use the product should be ~~recorded~~ **received in writing** by the manufacturer. **Following receipt of this written agreement, the qualified person may certify the batch for supply to this specific physician by reference to the regulatory filing, risk assessment and physician agreement.**  In addition to the above, when the out of specification product is administered to a trial subject, the impact of the use of an out-of-specification product in the clinical trial should be determined and notified to the sponsor.  **All i**nstances of administration of an out-of-specification product ~~to a clinical trial subject~~ should be notified to the relevant competent authorities. |
| 12.1 | 1820-1823 | It is suggested that this section could be used to broaden the terminology from ‘quality control’, which is typically associated with laboratory operations, to include ‘quality assurance’ and the responsibilities of the ‘quality unit’ or ‘person responsible for quality’ (as opposed to the ‘head of quality control’) | **12. Quality control and quality assurance**  **12.1. General principles**  Quality control is intended to ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations**; the quality unit, or person responsible for quality**, ~~but~~ must be involved in all decisions which may affect the quality of the product.  **These wider responsibilities are often referred to a ‘Quality Assurance’**  The person responsible for quality ~~control~~ should ensure that the premises and equipment where quality control operations are carried out are appropriate and maintained under suitable conditions and that the personnel working under his/her responsibility is adequately trained. In-process controls may be carried out within the production area provided they do not carry any risk for the product.  The person responsible for quality ~~control~~ supervises all quality control procedures. In particular, ~~it assumes~~ **they assume** responsibility for the following tasks: |
| 12.1 | 1836-1838 | Suggest additional wording to make it clear that the ‘control’ required here is not necessarily an analytical test, but is more likely to be based on documentation. | In case of autologous products or donor-match situation, a control should be carried out to verify the match between the origin of the starting material and the recipient**, e.g., through confirmation of labels or other traceability documentation.** |
| 12.3 |  | There is no mention in this section currently about the use of reference standards or alternative means of demonstrating the ongoing suitability of analytical methods | Suggest adding statement such as:  **Where possible, product reference standards should be implemented to aid understanding of the consistency of product quality. Where it is not possible to implement a specific product reference standard, e.g. for an autologous cell-based product, it is the manufacturer’s responsibility to assure sufficient product consistency and characterisation. Consideration should be given to monitoring analytical methods through the use of an external quality assessment programme.** |
| 12.3 | 1954-1955 | Confusing clause in this sentence: “Results of parameters identified as a quality attribute or as critical…” | Suggest text change as follows:  **Test r**esults of ~~parameters identified as a quality attribute or as~~ critical **quality attributes** should be trended and checked to make sure that they are consistent with each other. |
| 12.3 | 1958-1970 | The technical transfer of testing methods does not distinguish between requirements for investigational vs. authorised ATMPs. We consider that the expectations given here should be specific to authorised ATMPs or certainly not prior to Phase III. | Suggest change section title to:  Technical transfer of testing methods **for authorised ATMPs** |
| 12.3 | 1958ff | There is no text here covering the qualification of test methods at the receiving laboratory prior to the transfer protocol which would focus on equivalence. | Suggest include an extra bullet:  **Qualification of the test method at the receiving laboratory prior to the technical transfer** |
| 12.4 | 1972 | For certain products, e.g. autologous products where the entire quantity of each batch is dosed back to the patient, it might not be possible to have an ongoing stability monitoring program. This would be an exception agreed to as part of the marketing authorisation. | After the marketing authroisation is granted, **unless justified and agreed otherwise**, a programme should be implemented... |
| 12.4 | c. 1987 | Following on from the above, suggest that where it is not possible to perform ongoing stability studies, the proposed shelf life should be covered as part of the process validation with consideration of the use of surrogate material batches to provide ongoing supporte | Suggest new sentences in between current sentences in line 1987 or nearby:  ... otherwise justified. **For autologous products where ongoing monitoring using finished product batches is not appropriate, the shelf life should be covered as part of process validation. Consideration should be given to manufacturing periodic batches with surrgogate materials for additional ongoing assurance.** Out of specifications... |
| 14.2 | 2046-2053 | This section is very light cf.the expectations in EudraLex Volume 4, Part I, Chapter 8.  It is suggested that, as a minimum, the following should be added:  The need for periodic testing of the recall process;  The need for appropriate segregation of recalled product;  The need for a report to be issued following a recall | Suggest adding:  To the end of current text in line 2049:  **The recall procedure should be regularly reviewed and updated when necessary. The effectiveness of the recall arrangements should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should cover the possibility of recall both within and outside of normal office hours. Consideration should be given to performing mock recalls. These evaluations should be documented and justified.**  Before the current text in line 2050:  **Product returned due to recall should be clearly identified and segregated until the recall has been concluded. A formal disposition of all recalled product should be made and documented.**  After the existing text:  **Following a recall, a report should be issued, covering product reconciliation, other actions taken and lessons learnt from the event.** |
| 15 | 2054-2073 | This topic is covered by existing EU GMO guidelines. We suggest that this section kept at very high level in this GMP guide and cross-reference made to Directive 2001/18, Directive 2009/41,CHMP /GTWP/125491/06 and EMEA/CHMP/473191/06 or their successors for detailed requirements on environmental control of GMO to avoid duplication and further risk of divergence) | We suggest to replace the text of section 15 with cross references to applicable GMO guidances, i.e.,: Directive 2001/18, Directive 2009/41,CHMP /GTWP/125491/06 and EMEA/CHMP/473191/06 or their successors for detailed requirements on environmental control of GMO. |
| 15 | 2064 - 2066 | There is question as to whether ‘replication limited’ should be ‘replication incompetent’ and around the absence of clear definition. It is suggested that in the context of this guidance the emphasis is on preventing the formation of new recombinant vectors and the wording could thus be simplified. | Where ~~replication limited~~ **viral** vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent **or new** recombinant vectors. |
| 16.1 | 2076/77 | Although these activities can be performed at the administration site and are thus outside a GMP environment, it should perhaps be noted that this does not mean they can be carried out in an uncontrolled environment since these activities will typically require an aseptic or closed environment. | Reconstitution activities can be performed at the administration site *(e.g.* in hospital pharmacies **with appropriate facilities**) outside a GMP environment. |
| 16.1 | 2083 | It should be specified that all these examples are in cases where activities are in accordance with instructions from the marketing authorisation holder or clinical trial sponsor, to prevent clinics performing activities which have not been assessed for impact on product quality | The following are examples of reconstitution activities relevant for ATMPs**, where conducted in accordance with instructions from the marketing authorisation holder or clinical trial sponsor**. |
| 16.1 | 2085-2087 | Although we acknowledge and appreciate the added flexibility afforded to ATMPs compared with other medicinal products, we consider that this bullet goes significantly beyond ‘reconstitution’ and that steps such as washing, buffer exchange and centrifugation should not be included. | Thawing, ~~washing, buffer exchange, centrifugation steps necessary to remove preservation solution (~~*~~e.g.~~* ~~DMSO), removal of process related impurities (residual amount of preservation solution, dead cells) including filtering~~ |
| 16.1 | 2090/91 | Mixing with ‘patient’s own cells’ and ‘adjuvant and/or other substances’ are terms which are both broad and loose with risk of interpretation being too wide. It is suggested that these should be more clearly defined and tied to regulatory submission. | Mixing the product with patient’s own cells, with an adjuvant and/or with other substances added for the purposes of administration (including matrixes) **as specified in the marketing authorisation/clinical trial authorisation**. |
| 16.2 | 2105/2106 | Suggest that it is made clear that ‘appropriate studies’ should include stability | *i.e.* through appropriate studies**, including stability evaluation,** it should be demonstrated that the specified reconstitution process is… |
| 17 | 2116-2129 | It is unclear whether this applies only to a fully automated process, or to automated steps in a manufacturing process that is not fully automated. Please clarify. | Suggested text:  **This section applies in full to the automation of the production of the final ATMP. Some production processes may consist of a mixture of automated and non-automated steps, in which case sub-sections 17.2 – 17.5 should be applied as appropriate.** |
| 17.6 | 2199 - 2203 | There is a missing Section reference in Lines 2200/01, which we suggest is Section 11 or, more specifically, 11.3.  However, even with this, the sentence does not make sense as currently written and requires further elaboration for clarity, i.e., which aspects of the QP role are seen as possibly being different in the context of automated production?  The possibilities of a QP being responsible for more than one site and reliance on audits conducted by third parties exist generally and are not seen as being particular to automated systems and it is suggested that the real opportunity here is to allow for administration decisions by personnel other than QPs within a quality system that has been approved by a QP (see general comments). | Some specific elements described in Section **11** may **need to** be considered **and defined** in the context of automated production of ATMPs**.**~~, such as the possibility that the same QP is responsible for more than one site, or the possibility to rely on audits conducted by third parties~~. **[see general comments for proposals around enhancement of this section]** |

**Typographical errors and non-technical editorial suggestions**

| **Section** | **Line no.** | **Comment / Rationale** | **Proposed change / suggested text** |
| --- | --- | --- | --- |
| 1 | 112 | Suggest change ‘an adequate’ to ‘a good’ | There is ~~an adequate~~ **a good** documentation system... |
| 2.1 | 155-158 | Suggested wording change for better clarification | It…….and of the product **and its application**. |
| 2.1 | 167 | Typos – ‘type’ should be ‘types’; ‘operators’ should be ‘operations’  Also suggest wording change for easier reading and clarity. | The risk-based approach is applicable ~~in an equal fashion~~ to all ~~type of~~ operations **and settings**. |
| 2.2 | 200 | Suggest changing the word “study” to “data” | “...may compromise the use of the **data** in the context...” |
| 2.3.1 | 236 | Suggested wording change to clarify that the risk referred to in this line is risk to patient | Additionally, it is important to take into account the level of **potential** risk **to the patient from** ~~of~~ the raw material due to… |
| 2.3.1 | 240 | The qualification of suppliers is not the only control strategy, so the ‘i.e.’ should be ‘e.g.’ | (~~i.e.~~ **e.g.,** qualification of suppliers) |
| 2.3.3 | 293-295 | Suggested wording change for better | It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing of ATMPs is done under aseptic conditions, ~~also~~ **even** when the manufacturing process does not involve substantial manipulation |
| 3.3 | 396-397 | Consider moving the line:  *“For every worker in a grade A/B area, clean (sterilised) protective garments should be provided at each work session.”*  To the section specifically for Grade A/B (lines 387-394) to make the requirement more obvious |  |
| 4.2.2 | 530/560 | The two tables below lines 530 and 560 are very similar and text can probably be edited to require only one table. |  |
| 4.2.2 | 531 | It is suggested to replace the word “fibres” with “particles” as this is a more generic term | ...to generate ~~fibres~~ **particles** should be... |
| 4.2.3 | 591 | Typo that changes meaning – ‘adapted’ should be ‘adopted’ | ... may be ~~adapted~~ **adopted** after validation... |
| 4.4 | 643 | There are no further details available in Section 12.1 regarding quality control premises, so suggest the last sentence is deleted. | ~~Further details are available in Section 12.1~~ |
| 6.2 | 726 | Suggest rewording to not use the phrase ‘It is recalled that’  Also, typo – ‘into’ should be ‘to’ | It ~~is recalled~~ **should be noted** that changes ~~into~~ **to** the... |
| 6.2 | 765-766 | Suggest reformat to make clear that batch definition is required in all cases and that the sentence about autologous products is a clarifying note. | (vi) Batch definition.  **NOTE:** For autologous and allogeneic 1:1 products, each unit should be considered a distinct batch. |
| 6.2 | 781 | Suggest rewording to not use the phrase ‘It is recalled that’ | It ~~is recalled~~ **should be noted** that, for authorised ATMPs… |
| 6.2 | 807-809 | The line:  *Where different manufacturing steps are carried out at different locations under the responsibility of different QPs, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.*  Appears to be in the wrong place. | Suggest this is moved to the earlier section on the Product Specification File (Lines 786 – 799) |
| 6.6 | 880 | Suggest title is amended to reflect that it is about data/records of traceability rather than activities undertaken to assure material traceability | Traceability **data** |
| 7.3 | 982, 991, 997, footnote 16 | Reference citations should be consistent throughout the document. In some cases a directive is referenced by just the year and number, e.g., Directive 2004/23, whereas in other instances the full reference is used - Directive 2004/23/EC | Directive 2004/23/**EC**; Directive 2002/98/**EC** |
| 7.3 | Line 1032/ Footnote 17 | It is suggested to add reference to the blood directive as well as is sometimes source of the starting material | 17Donation, procurement and testing of cells and tissues **and blood-derived cells** are governed by Directive 2004/23/EC **and Directive 2002/98/EC, respectively**. |
| 8 | 1083 | Suggested to replace the word “reagent” by “material” as used thus far in this guidance. | ...(e.g., ~~reagents~~ **materials** of biological origin**)…** |
| 9.1 | 1140 | Word missing | In **the** case of investigational ATMPs… |
| 9.2 | 1166 | Suggest ‘appropriate’ is a better word than ‘adequate’ | The control strategy should be ~~adequate~~ **appropriate** having regard to the risks. |
| 9.7 | 1383 | Suggest to add “labelling” to the title as this is covered in this section as well. | Packaging **and labelling**” |
| 10.3 | 1564 | Suggest adding wording toindicate that this is the minimum requirement. | The following**, as a mínimum,** should also be specified in the protocol: |
| 10.3 | 1602 | Typo – ‘ration’ should be ‘ratio’ | ... benefit-risk ratio~~n~~ for the patient... |
| 10.3 | 1628 - 1629 | Suggest rewording to not use the phrase ‘It is recalled that’ | It ~~is recalled~~ **should be noted** that for the clinical trial to be used… |
| 11.1 | 1650 | Reference to a Section 11.3.3, which does not exist in this document. | Suggest delete the early part of this sentence:  ~~Without prejudice to Section 11.3.3, batches~~ **Batches** of medicinal products... |
| 11.3 | 1744, footnote 26 | Typo in footnote #26: feature should be *features.* | 26ATMPs....exempted from the safety ~~feature~~ **features** in accordance… |
| 11.3.1 | 1775 | Typo – ‘side’ should be ‘site’ | … from one trial ~~side~~ **site** to another… |
| 11.3.2 | 1790-1792 | Suggest to add in this sentence for clarification “product for administration” | Ä procedure… of the product **for administration**. |
| 12.1 | 1851 | Typo - procedure description should be *procedural* description | (e.g., ~~procedure~~ **procedural** description or records…) |
| 12.3 | 1937 | Typo –critically should be *criticality* | ... and the ~~critically~~ **criticality** of the test… |
| 16.2 | 2114 | Typo – ‘constituation’ should be ‘reconstitution’ | Likewise, when the **re**constituation requires... |
| 17.2 | 2157 | Suggest replace ‘adequate’ with ‘appropriate’ | ~~Adequate~~ **Appropriate** maintenance |