**Submission Date: September 26, 2016**

Submission of comments on 'Good manufacturing Practice for Advanced Therapy Medicinal Products' (EMA/…/…)

Comments from:

| Name of organisation or individual |
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| ORGANIZATION: INTERNATIONAL SOCIETY FOR CELLULAR THERAPY |

 *On behalf of the International Society for Cellular Therapy, please find attached consolidated comments prepared by the ISCT Europe Legal & Regulatory Affairs (EU LRA) Committee and the ISCT Europe Regional Executive Committee. The members of these Committees represent the collective voice of academic hospitals, institutions, biopharmaceutical, and manufacturing companies of all sizes operating in Europe. Comprised of over 1300 members globally, ISCT currently has over 225 European members.
For reference, please find below links to the membership rosters for both Committees:*

* [***ISCT EU LRA***](http://www.celltherapysociety.org/?page=LRACommitteeEurope)
* [***ISCT EU Regional Executive Committee***](http://www.celltherapysociety.org/?page=RegionalCommittees#Europe)

***About the International Society for Cellular Therapy***

*Established in 1992, the International Society for Cellular Therapy (ISCT) is a global society of clinicians, regulators, researchers, technologists and industry partners with a shared vision to translate cellular therapy into safe and effective therapies to improve patients’ lives worldwide.*

*ISCT is the global leader focused on pre-clinical and translational aspects of developing cell-based therapeutics, thereby advancing scientific research into innovative treatments for patients. ISCT offers a unique collaborative environment that addresses three key areas of translation: Academia, Regulatory and Commercialization. Through strong relationships with global regulatory agencies, academic institutions and industry partners, ISCT drives the advancement of research into standard of care.*

*Comprised of over 1300 cell therapy experts across five geographic regions and representation from over 50 countries, ISCT members are part of a global community of peers, thought leaders and organizations invested in cell therapy translation. For more information about the society, key initiatives and upcoming meetings, please visit:*[*www.celltherapysociety.org*](http://www.celltherapysociety.org/)*.*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
| **ISCT** **MAIN COMMENT**  | The position of the ISCT on the consultation document “Good Manufacturing Practice for Advanced TherapyMedicinal Products” is as follows: ISCT is concerned with the possibility that this guideline for GMP requirements to be applied by all manufacturers of ATMPs will create a double standard, particularly on the national level. We do not have a unique position on the character of this document (to be standalone guidance or to be an annex of the current GMP guideline). Nevertheless, we recommend that either the standalone document will be extended to include more details and become aligned, as applicable, with the EudraLex Volume 4 as well as Annexes (along with their revised versions), including cross-reference to relevant sections; or if commonalities significantly outweigh the differences, the exceptions could be readily addressed through appropriate wording in an ATMP Annex to EudraLex Volume 4. In any case, we consider critical its integration in EudraLex as well as its inclusion in PIC/S. Moreover, ISCT strongly recommends the European Commission to utilize mechanisms in place for coordination and collaboration between the EMA and the National Competent Authorities (NCAs) to avoid different interpretations by the inspectors at the different NCAs. To avoid the risk of discrepancies in the interpretation of these standards among manufactures and inspectors in each member state and to insure harmonization among member states, it should be established that this guideline will prevail for ATMPs, in case of divergent requirements, as compared to the current GMPs and relevant annexes. |  |
| **ISCT** **GENERAL COMMENT #1** | A glossary of terms and list of abbreviations should be included into the document. Such a glossary of terms should e.g. clarify roles and responsibilities like manufacturer, sponsor, the special role of CDMO’s (where sponsor and manufacturer are not the same legal entity). |  |
| **ISCT** **GENERAL COMMENT #2** | The flexibility introduced in the GMP for ATMP with the risk-based approach applicable to numerous areas, specificities for investigational/early phase ATIMPs and for non-substantially manipulated ATMPs is welcomed. However, as regards the "risk-based approach" as described in chapter 2, there seems to be a semantic question as the notion of “risk-based approach” has been introduced by Regulation 1394/2007 and implemented in Directive 2001/83, annex 1, part IV, where it is stated: “*Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the ‘Introduction and general principles”…* In chapter 2 of this version, it is very likely the “risk-based approach” is used in the meaning of risk- assessment of risk evaluation, as it is recommended in ICH Q9 and Q10. It is proposed to modify the title of the chapter to read "risk-assessment approach" to make it clear that any specific flexibility in the application of GMP rules for ATMP should be based on prior risk-analysis as ATMPs represent a unique class of medicinal products with respect to their manufacture, quality control and risk profile. |  |
| **ISCT** **GENERAL COMMENT #3** | In the current version, there seems to be some statements and recommendations that relate mainly to development, validation and assessment of the products (drug substance or drug product) and do not concern the GMP aspects when it is to transfer, implement and carry-out on a routine basis a new process into a GMP manufacturing site. It is proposed to delete paragraphs (they will be identified in the list of “specific comments on text”) which are not dealing with GMP considerations and make, in the introduction a key message to insist on the need for the manufacturer to transfer only processes that have been developed, validated and authorised, as it is well stated, in line 137-143 of the introduction. |  |
| **ISCT** **GENERAL COMMENT #4** | The exceptions for Investigational ATMPS should be summarized at the end of each of the 17 chapters, in order to have a more comprehensive reading within each of the chapters and also to make the differences more feasible. |  |
| **ISCT** **GENERAL COMMENT #5** | We suggest a meeting with all relevant stakeholders. We think this is crucial to hear the pros and cons and decide on a path forward together with the European Commission, EMA IWG, Academia, Industry, Hospitals, and other stakeholders. |  |
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1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 108 and 112-119 |  | The introduction on the importance of quality and its role on ATMP safety and efficacy profile are very well taken, but the objectives of GMP may be better defined as the objective of “assessing GMP compliance”. **Proposed change (if any):** Line 108: “The main objective of assessing a GMP compliance is to find evidences that:…” |  |
| 133-136 |  | The term “authorized” ATMPs may be confounding since also investigational ATMP have to be authorized, even though in a clinical trial setting. Therefore, it is suggested to use the term “for the market” ATMP instead of “authorized” ATMP”.It is very welcome that in this new version of the document the previous request made by ISCT to exclude by these guidelines ATMPs produced under the rules of hospital exemption has been accepted. Nevertheless, despite no clear reference is made to the ATMPs produced under Hospital Exemption, a clear statement of exclusion is still missing. **Proposed change (if any): Suggested text is underlined**To add, following line 170: “Manufacturing of ATMPs under the hospital exemption is not within the field of application of this consultation document since it is under the responsibility of each Member State National Competent Authorities to regulate and define standards for this activity. Meanwhile, article 28 of Regulation 1394 requires for HE ATMPs quality standards equivalent to ATMPs for which authorization is required to safeguard patients”. |  |
| 167 |  | The term “operators” should be clarified. It should be interpreted as manufactures, developers or others. **Proposed change (if any):** To replace operators by a more precise term. |  |
| 198-205 |  | The need to ensure quality also during the early phase of development is extremely important, but, as already stated in General Comment #2, this issue is relate mainly to development, validation and assessment of the products (drug substance or drug product) and does not concern the GMP aspects when it is to transfer, implement and carry-out on a routine basis a new process into a GMP manufacturing site. As in our understanding, it is not the responsibility of the manufacturer to assess the relevance of the risk-based approach followed in the development of an IMP. The issue of the need for a mature quality system starting from the early phases of pharmaceutical development is a consideration that may be better located in the introduction rather than in this specific paragraph since it deals with the more general objective of assessing the adequacy of the pharmaceutical quality system. **Proposed change (if any):** See General Comment #2. |  |
| 206-211 |  | There might be overlapping and confusion between the clinical trial (CT)/marketing authorization (MA) assessment and the compliance of ATMP manufacturing to GMP: it seems that at the level of assessment of an authorisation dossier (CTA or MAA), it will be verified that there is not only a proper manufacturing process but also a relevant quality control strategy. See also comments to L243- 257 and L303-313**Proposed change (if any):** There should be adequate documentation of the risk-based approach followed to define the manufacturing process and the process controls and a sound demonstration that the measures applied are adequate to ensure the quality of the product.  |  |
| 213-214 |  | Whether an RBA is appropriate for an authorized ATMP during its development or not should be clarified. It is our understanding that, the RBA needs to be applied already during the development of the authorized ATMP. Within the marketing authorization it will be approved by the relevant authorities. **Proposed change (if any): Suggested text is underlined**To delete: “For authorized ATMPs, the starting point for the application of the risk-based approach is the marketing authorization” and to substitute with: “The risk-based approach can be applied also during the development of “for the market” ATMP”. |  |
| 237 |  | The importance of assessing different risks for basal media vs. cytokine-containing media and the importance of raw materials being in contact with the cell product is an important issue, but it is suggested to change some words to make the sentence and the examples more clear.**Proposed change (if any): Suggested text is underlined** “Additionally, it is important to take into account the level of the risk related to raw materials due to their composition thereof (e.g. higher risk when a culture media contains cytokines vs.low risk with a basal media without cytokines) or the use thereof in the manufacturing process (e.g. higher risk if the raw material comes in contact with the cellular product as a starting material or in the intermediate phases of manufacturing).” |  |
| 243-257 |  | The issues of an rational approach to release testing is very welcome, but, as for line 206-211 and (below) for lines 303-313, the border between the clinical trial (CT)/marketing authorization (MA) process and the compliance of ATMP manufacturing to GMP is not well defined by this sentence.**Proposed change (if any): Suggested text is underlined**Line 248:”….In this case there should be adequate evidence from process validation that the manufacturing process and the in-process controls are adequate to obtain a final product with the defined specifications.” |  |
| 268-272 |  | The issue of particulate matter test is of special interest in cell therapy. It has been recently explored by some members of the International Society for Cellular Therapy (Process and Product Development Subcommittee, USA) and their recommendations for best practices have been described in *Clarkes et al, Cytotherapy 2016, 18; 1063-1076*. Indeed, visual inspection, that is already problematic for biologics due to subjectivity and dependence on trained personnel, becomes even more problematic for cell therapy products. For developers of cell therapy products, it will be prudent to develop a visual inspection procedure that can detect visible particulates within an opaque liquid in a water/placebo run. **Proposed change ( if any):**As particulate matter test in a final product made of a cell suspension is quite problematic, an RBA with appropriate mitigation measures to control the sources of particulate (e.g. classification of the manufacturing area, positive pressure environments to have airflow from clean to less clean areas, airflow patterns and airflow velocity, filtered air with HEPA filters or other, suitable facilities, areas, equipment, and materials, trained personnel, environmental monitoring etc.) can support the possibility to perform a particulate matter test on water/placebo run instead than on the final product. |  |
| 284-290 |  | The possibility to manufacture “non-substantially manipulated ATMPs” in premises “validated” for transplantation purposes needs clarification.If validation means “to make legally valid”, then, the meaning of sentences in lines 288 and 290 is that those premises already licensed to process cells/tissues may be automatically considered as licensed also for non substantially manipulated ATMPs. It should be clarified that, as this particular category of ATMPs are regulated under directive 2001/83 EC but have the same characteristics as non-substantially manipulated transplant/transfusion products used for the same essential function in the donor and the recipient, which are regulated under Directive 2004/23/EC, as amended, or Directive 2002/98/EC, the technical requirements for donation, procurement, **manufacturing**, storage, and distributions of these products are appropriately covered by cells and tissue standards. However, the GMP manufacturing license should remain under the responsibilities as laid down in Directive 2001/83 EC. Consequently, the manufacturing authorization of this category of ATMPs should be managed under directive 2001/83 EC as any other pharmaceutical products and no “automatic licensing” should be permitted.**Proposed change (if any): Suggested text is underlined**Delete line 284 to 290 and substitute with : “Non substantially manipulated ATMPs are regulated under directive 2001/83 EC but have the same characteristics as non-substantially manipulated transplant/transfusion products used for the same essential function in the donor and the recipient, which are regulated under Directive 2004/23/EC, as amended, or Directive 2002/98/EC, the technical requirements for donation, procurement, manufacturing, storage, and distributions of these products are appropriately covered by cells and tissue standards. However, the GMP manufacturing license should remain under the responsibilities as laid down in Directive 2001/83 EC. Consequently, the manufacturing authorization is required also for this category of ATMPs as per directive 2001/83 EC”. |  |
| 295-299 |  | This section states that a RBA is required when the manufacturing operations take place in an “open environment” other than grade A with surrounding grade B areas. Since the concept of “open environment” needs clarification by itself, it is proposed either to shift this sentence in Section 4.2.2. or to define closed systems within this paragraph. It is also suggested to rephrase as follows:**Proposed change (if any):**Line 295: “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 and particular considerations should be paid to the use of closed or almost-closed system and to the time that the product is exposed to the environment. There should be a clear documentation that the implemented control measures are adequate to ensure the sterility of the final product.” |  |
| 303-304 |  | There is a need for clarification regarding those "elements of GMP" (line 303) that are intended to ensure the quality, safety and efficacy which are not addressed under other legislative frameworks”**Proposed change ( if any)**:To add some examples |  |
| 303-313 |  | The requirements for the processing of cell-based medicinal products considered medicinal products in virtue of its indication (according to criteria of same/different essential function) but which are not subject to substantial manipulation should be those established in Directives 2004/23/EC and 2006/86/EC for the processing of cells and tissue for transplant in tissue establishments, not only related to premises and equipment, but in general. It is believed that, from a risk/benefit analysis, it is disproportionate to ask for the same product characterization, process validation and quality control requirements as in the case of substantially manipulated medicinal products. Especially disproportionate seems to ask for quality controls according to GMPs in some cases in which the experience has extensively demonstrated the safety of practising quality controls under the requirements established in Directives 2004/23/EC and 2006/86/EC for the processing of cells and tissue for transplant. As an example, the use of non-substantially manipulated cell fractions from bone marrow. They are a group of cell products which have a double classification either as a transplant -when administered for the treatment of patients with hemato-immunologic diseases- or as a medicinal product -when administered for the treatment of diseases different from the formerly mentioned. If the accumulated experience, throughout more than 50 years in the field of hematopoietic progenitor transplantation (HPT), has demonstrated the safety of the quality standards applied to the tissue establishments and the cell and tissue processing for transplant, it does not make sense to increase those manufacturing standards and demand greater quality controls for the same product just because the indication has changed. And specially, if we take into account that the HPT is generally allogeneic and it is performed in immunosuppressed patients, whilst the cell therapy with the same product for other diseases different from HPT is normally autologous and used in immunocompetent patients. In this regard, see also the comment to lines 284-290.**Proposed change (if any)**: To eliminate this paragraph. |  |
| 306-309 |  | The concept of the need for product characterization, validation and quality controls also for non-substantially manipulated products has been already well expressed in the introductory remarks. **Proposed change (if any)**: To delete the sentence. |  |
| 309 |  | The adequacy of quality data in the clinical trial or marketing approval application is a very crucial point, but it is our understanding that a clinical trial will never be approved without prior assessment of a quality dossier in which characterisation, manufacturing process and quality controls will be described. **Proposed change (if any)**: To delete the sentence. |  |
| 322-325  |  | The reference to the possibility to manufacture ATMPs upon an adequate RBA in class A with other-than-class B surround has been already well stated in line 396-397. To make compatible to what previously stated it is requested to specify that the surround can be in class C or D.**Proposed change (if any)**: **Suggested text is underlined**Line 323 “…in clean area of class C or D….” |  |
| 328-333  |  | The recognition of the possibility of reduced frequency of validation and qualification in the case of very low manufacturing activity is welcome, but there should be the need to clarify the meaning of “very low manufacturing”.**Proposed change (if any)**:  |  |
| 370 |  | Eating, drinking, chewing, smoking and applying cosmetics (e.g. hand cream) should not be allowed.**Proposed change (if any):Suggested text is underlined**Eating, drinking, chewing, smoking, or applying cosmetics (e.g. hand cream) as well as the storage of food or personal medication should be prohibited in the production and storage area. |  |
| 435-649  |  | It is suggested to depart from, e.g. a class A grade for a given operation based on a well conducted risk-analysis. Apparently in reading lines 520-526 this is not possible for Gene Therapy, but what about cell or tissues-based products? This may be seen as a feasible approach.**Proposed change (if any):**Part of the "flexibility" could be envisaged as regard class grade instead of a relatively strict and non-negotiable approach. |  |
| 461 |  | This statement should be expanded to provide possibilities of such as segregation in time and use of closed systems within one area. **Proposed change (if any):**Amend this section to include the possibility of segregation in time and use of closed systems for manufacturing ATMPs. |  |
| 463-465& 472-474 |  | 463-465: “In the case of manufacturing of investigational ATMPs, it is accepted that the same area is used for multiple purposes, provided that appropriate cleaning and procedural controls are in place to ensure that there is no carry-over of materials or products, or mix-ups.”It’s redundant with:472-474: “In the case of investigational ATMPs, where there are no separate production suites, a thorough cleaning and decontamination procedure should take place before any subsequent manufacturing in the same area can occur.”**Proposed change (if any): Suggested text is underlined**462:In the case of manufacturing of investigational ATMPs, it is accepted that the same area is used for multiple purposes, provided that appropriate cleaning, decontamination and procedural controls should take place before any subsequent manufacturing in the same area can occur to ensure that there is no carry-over of materials or products, or mix-ups.472: In the case of investigational ATMPs presenting a known microbiological risk where there are no separate production suites, a thorough cleaning and decontamination procedure should take place before any subsequent manufacturing in the same area can occur. |  |
| 483 |  | Separation in time and space (put other things away so nothing can splash on them or touch them). |  |
| 521 |  | Concentration of vector with possible aerosolization of high titer vector is not taken into account in these recommendations, but should be. |  |
| 524 |  | This statement should be further clarified to include cases where production is done in critical clean area of grade A with a background clean area of grade B since most of GMP facilities are A/B and tissue and cells labs are A/B. **Proposed change (if any):Suggested text is underlined**The expansion phase before the sterilizing filtration can be performed in a critical clean area of grade A with a background clean area of grade B or C. |  |
| 546 |  | Monitoring of clean rooms should be performed “in operation”. Usually monitoring in operation is done only for grade A zones.**Proposed change (if any):** To substitute “clean rooms” with “grade A zones”. |  |
| 553-555 |  | The degree of environmental control of non-viable particulate and the selection of the monitoring system should be adapted to the specific risks of the product and of the manufacturing process.**Proposed change (if any): Suggested text is underlined**“The degree of environmental control of non-viable particulate and the selection of the monitoring system should be adapted to the specific risks of the product contamination and of the manufacturing process”. |  |
| 561 |  | Continuous particle monitoring during manufacturing for all classes is highly questionable. Most importantly is stating that the clean rooms need to be qualified before manufacturing and stability of the room needs to be demonstrated.**Proposed change (if any):**It should be clearly written that particle monitoring in class B clean rooms must not be performed for the full duration of critical processing (only for class A). |  |
| 566-567 |  | This statement: “effectiveness of the segregation between Grade A and B zones”, is unclear.**Proposed change (if any):** Further explanation is required to clarify what is the meaning of “effectiveness of the segregation between Grade A and B zones” |  |
| 572-574 |  | If you are doing a sanitization, you are doing a planned activity, so any off-limit measurement is planned and justified. |  |
| 581 |  | ‘In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration is an important diagnostic tool for early detection of failures’. **Proposed change (if any):** Please provide a more detailed explanation on this statement particularly in regard to the term ‘detection of failures’. |  |
| 593-596 |  | Monitoring viable particles in closed production system might be impossible (e.g. SEPAX system for bone marrow mononuclear cells selection).**Proposed change (if any):**To modify the example as follows: e.g. in a closed production system the monitoring of viable particles might be impossible. |  |
| 601 |  | Error in the heading of the last two columns.**Proposed change (if any):** “CFU/plate” in the heading of the last column should be moved to the previous. |  |
| 615 |  | How can you maintain the cleanliness of a negative pressure area? This is only possible when laminar air flow with low returns is applied. Needs to be seriously contemplated. |  |
| 650-690 |  | Equipment: 5.1 General principles and 5.2 Maintenance cleaning repair: The principles in GMP Chapter 3 on Equipment (3.34-3.44) and Annex 15 on Qualification and Validation do apply to ATMPs, and most of the information in section 5.1 and 5.2 is redundant and should be deleted for clarity, in case this guideline is an annex to current GMPs. |  |
| 660-661 |  | Guidance on aseptic connections should be replaced to section 4 Premises or section 9 General Principles. |  |
| 691-914 |  | Documentation: The guidance in GMP Chapter 4 on Documentation does apply to ATMPs, and most of the information in section 6 is similar and should be deleted for clarity, in case this guideline is an annex to current GMPs. |  |
| 691-793 |  | In line with current GMP guidance, it should be made clear in this chapter that the content of the documentation to be used and generated during the GMP operations should be based on the CTA or MA dossier and the role of the GMP documentation should essentially to assure quality compliance. |  |
| 735-736 |  | The meaning of “anatomical environment” is not obvious, therefore more clarification is required. |  |
| 759 |  | We consider unnecessary to specify rejection criteria for materials and products. All materials and products not meeting release criteria must be rejected.**Proposed change (if any):** To eliminate “and rejection”. |  |
| 765-766 |  | The term “unit” should be defined/modified as for an autologous product; one batch can also be constituted of several units (e.g. freezing of several vials from the same pool of cells).**Proposed change (if any): Suggested text is underlined**“(vi) Batch definition. For autologous products, all units coming from the same starting materials and processed in the same run should be considered a distinct batch.” |  |
| 796-797 |  | The effectiveness of the blinding procedures should be verified.” This is not specific to ATMPs, and verification of blinding procedures is not obvious and should be explained elsewhere in GMPs if needed.**Proposed change (if any):** Delete this sentence”. |  |
| 917 |  | It is proposed to state, at the introduction of the chapter, that "raw material" and "starting material" are defined according to the definition provided in Regulation 1394/2007 and part IV of annex I of Dir. 2001/83 as amended. |  |
| 930-951 |  | The first paragraphs on raw materials, although accurate from the development and authorisation point of view, should not appear here as it is clearly not the responsibilities of the manufacturer "to insure the suitability…”.Indeed, according to both Annex 1, part IV of Dir. 2001/83 and the EP General Chapter on raw materials, it is the responsibility of the sponsor to identify and set the quality specifications for raw materials (be they critical). The manufacturer, according to the GMP rules, should apply what has been laid down and authorised in the MA or CTA dossier and in no way should take any responsibility on those raw materials.**Proposed change (if any):** To delete lines 931-933 and replace them by lines 944 up to “with the supplier" in line 946.Continue with the text from lines 934- until "grade are available" in line 938 and go to: "It is the responsibility of the sponsor or marketing authorisation holder to establish quality requirements for raw materials according to the specifications declared in the dossier (CTA or MA)”. Delete lines 938-951. |  |
| 944-951 |  | Another occurrence of the comment above (lines 930-951): it is not the to the ATMP manufacturer to establish quality requirements, nor to make the assessment whether a specific raw material is critical or not. **Proposed change (if any): Suggested text is underlined**“The sponsor or marketing authorisation holder should establish quality requirements (specifications) for raw materials (critical or not). It is the responsibility of the manufacturer to verify fulfilment of those specifications by the supplier(s). The specifications should be in compliance with the terms of the marketing authorisation or clinical trial authorisation”. |  |
| 968-974 |  | It is stated that “critical raw materials in the storage area should be appropriately labelled…. “. According to GMP, any material stored in a storage area should be well identified and properly labelled. It is also assumed that the label affixed by the supplier will be bearing the requested information. It is proposed to clarify this paragraph. **Proposed change (if any): Suggested text is underlined**“Raw materials in the storage area should be appropriately labelled. Upon reception and before storage manufacturer should ensure that the following information appear on the label and should complete them accordingly:” And continue with lines 970-974. |  |
| 981-986 |  | Regarding starting materials for ATMP, it is reminded that they are not only from human tissues and cells covered by directive 2004/23. They could also be derived from human blood and are covered by Dir. 2002/98.According to articles 15 and 22 of Regulation 1394/2007, the requirements for donation, testing and storage should be adapted to the regulatory status of the concerned starting material. It is proposed to clarify the paragraph on this aspect, so as not to exclude blood components as possible starting material.**Proposed change (if any): Suggested text is underlined**After the first sentence in line 981-982, add the following sentence:”Starting materials from blood component should be in accordance with Directive 2002/98/EC”.  |  |
| 987-993 |  | In line with previous comment on lines 944-951, the same modification should be made for starting materials, as indeed it is not the role of the manufacturer to establish quality requirements. **Proposed change (if any): Suggested text is underlined**Lines 987-993 should read: “The sponsor or marketing authorisation holder should establish quality requirements (specifications) for starting materials. It is the responsibility of the manufacturer to verify fulfilment of those specifications by the Tissue or Blood establishments designated by the sponsor as the supplier(s). Depending on the starting material(s) characteristics testing in addition to that foreseen in the relevant Directives may be required. The specifications should be in compliance with the terms of the marketing authorisation or clinical trial authorisation”.  |  |
| 1020-1026 |  | In line with previous comments on labelling of raw materials (Lines 968-974), it is proposed to re-organise the paragraph accordingly. For starting materials such as cell, tissues or blood components, they will be delivered with a duly conformed label as imposed by the relevant directive. **Proposed change (if any): Suggested text is underlined**Lines 1020-1026 should read: “Starting materials in the storage area should be appropriately labelled. Upon reception and before storage manufacturer should ensure that the label is conforming to the relevant directives. The label should, at least, bear the information relevant for traceability and be completed, where relevant, with the following information:”  And continue with lines 970-974. |  |
| 1030-1042 |  | This paragraph is not clear enough as regards the “initial processing steps of the starting materials”, as there may be some minimal manipulations which could be carried out, by the Tissue or Cell establishments, before considering that the starting material is entering the manufacturing process. As such there is no reason to consider that the starting material is always the immediate sampling/biopsy from the tissue or cell donor/patient. It is the responsibility of the sponsor (or the marketing authorisation holder) to define the “starting material” that will enter the manufacturing process. If there are some processing steps (not substantial manipulations) to be carried out immediately after sampling or prior to shipment to the manufacturing site, this has to described and authorised in the clinical trial authorisation or marketing authorisation dossier. By imposing in lines 1030-1032 that “initial processing steps are manufacturing activities…” seems not to be in line with the flexibility approach. **Proposed change (if any): Suggested text is underlined**Lines 1030-1042 should be amended as follows: Delete Line 1030 and replace by "Depending on the characteristics and definition of the declared starting material for the manufacture process, there may be some initial processing steps on the initial biopsy which can be carried out by the tissues or cell establishment, according to Directive 2004/23. It is accepted that those steps are not performed under GMP environment and it is the overall responsibility of the manufacturer …”. continue on line 1036 Delete lines 1040-1042. |  |
| 1044-1068 |  | The three paragraphs raise several issues for the use of xenogeneic tissues or cells. Most of them have to deal at the development level, as quality issues and should not be discussed as GMP issues. Only the points which are relevant for the GMP conditions should be discussed and clear recommendations made in terms of handling and usage of xenogeneic cells/tissues. It is indeed very likely that the aspect of animal sourcing, or breeding is not of concern for the ATMP manufacturers that are supposed to use only cells or tissues of animal origin, either as raw material or starting material. **Proposed change (if any): Suggested text is underlined**Keep the first sentence in line 1044-1046, but delete the next sentences: "The selection of donor animals …. up to founder animals similarly should not be used" and replace by "The selection of donor animals (including source, health status) should conform to the specification and characteristics described and approved in the clinical trial or marketing authorisation dossier”. Delete line 1053-1058. Delete lines 1059-1064 and replace them by: “The manufacturer of marketed ATMPs is responsible for auditing the supplier of xenogeneic cells/tissues and to make the necessary quality control upon receipt of the products. A look back procedure should be in place to inform the decision-making process on the continued suitability of the biological active substance or medicinal product in which the xenogeneic cells/tissues have been used or incorporated”. Keep the last two sentences starting at end of line 1064. |  |
| 1069-1133 |  | In the entire chapter 8 on seed lot and cell bank system, there is a problem of definition on the Master cell or Master virus seed. This chapter is essentially dealing with the GMP conditions under which the ampoule of those banks or seeds that will be used for production purpose under GMP, should be derived and qualified. However, in some sentences (they should be established under appropriate conditions (line 1074) or during the establishment of the seed lot and cell bank (line 1077 or lines 1085-1090) there is an ambiguity on what is meant by "establishment" and particularly establishment of the MCB.When one considers the official definition of MCB provided in ICH Q5D ("An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell") it appears that the first "bank" obtained from the selected clone cannot be obtained under GMP conditions as the selection of the desired clone and its first amplification is done at the research/development level. There is thus a need to clarify that the entire chapter on seed lot and cell bank system concerns the condition of obtention, qualification and use of the banks at the level of the manufacturing site.  |  |
| 1135 |  | According to the list of responsibility by the person responsible for QC (lines 1830-1846) the list of responsibility by the person responsible for manufacturing should be added.**Proposed change (if any):**A list of responsibility by the person responsible for manufacturing should be added. |  |
| 1135-1158 |  | The first 4 paragraphs of chapter 9.1 are covering the development and qualification of a given process and its QC strategy and as such should be discussed in relevant quality guideline, but not in a GMP document.**Proposed change (if any):**Production operations, including filling, packaging and -as applicable- cryopreservation need to follow clearly defined procedures designed to ensure the quality of the product, consistent production, and to comply with the requirements set in the relevant manufacturing and marketing/clinical trial authorization.Manufacturing processes and their control strategies should be reviewed regularly, and they should be improved as appropriate to reduce process variability and to enhance reproducibility at the different stages of the lifecycle.Any change to the manufacturing formula or manufacturing method should be managed in accordance with the principles set out in Section 6(2). |  |
| 1159-1162 |  | The QP responsibility in case of handling of deviations needs to be mentioned in this paragraph**Proposed change (if any): Suggested text is underlined**Please add in Line 1162: “The QP should control that any deviations have been appropriately authorized before releasing the final product”. |  |
| 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 (e.g., safety testing). **Proposed change (if any):**Identity testing should be carried out unless otherwise justified.In addition examples for ID testing or no ID testing should be added. |  |
| 1186 |  | Typo error.**Proposed change (if any): Suggested text is underlined** “The compatibility of labels with storage conditions (e.g. ultra-low storage temperatures, water bath) should be verified.” |  |
| 1188-1190 |  | The necessity of cleaning is mentioned in several paragraphs and does not necessarily need to be mentioned again in this paragraph.**Proposed change (if any):**To be deleted. |  |
| 1204-1205 |  | To have more clarification it should be explained that this paragraph is about the manufacture and qualification/release criteria of the gases used (ID, purity, impurities), as defined in the Ph. Eur. monographs, not about the safety implications of the gases when used, which is explained in the following paragraph or by other process steps. **Proposed change (if any):**Gasses that come in to contact with the product during processing should be compliant with the European Pharmacopeia in regard to manufacturing and Qualification and release criteria (ID, Purity, impurities). |  |
| 1206-1207 |  | 0.22 filters are recommended by the majority of incubators’ manufacturers to prevent the entry of particles with the gasses before HEPA-filtering them. **Proposed change (if any):**Gasses taken into the aseptic work place or that come into direct contact with the product should be passed through ~~micro-organism retentive~~ a filter to preserve the aseptic conditions.” |  |
| 1212-1214  |  | Line clearance is mentioned in several paragraphs and does not necessarily need to be mentioned again in this paragraph.**Proposed change (if any):**To be deleted. |  |
| 1216-1217 |  | The current wording may mislead the reader.**Proposed change (if any):**Special precautions should be taken to avoid mixing of autologous materials from different donors or other dedicated material. |  |
| 1224 |  | As this paragraph is about prevention of cross-contamination and sterilisation does not prevent cross-contamination this sentence can be deleted.**Proposed change (if any):**Delete sentence which starts in line 1224 and ends in line 1226. |  |
| 1230 |  | Especially during manufacturing of clinical ATMPs low batch numbers are produced, therefore, also the timely segregation should be mentioned. And as an example cryo-storage racks should be added.**Proposed change (if any): Suggested text is underlined** In line 1230 add: “i.e. campaign production, cryo-storage rack “. |  |
| 1244-1245 |  | Not only for autologous but also for allogeneic products the risk for cross-contamination needs to be covered.**Proposed change (if any):**Sentence which begins in line 1244 and ends in line 1245 can be deleted. |  |
| 1267-1274 |  | In line 1267-1268, closed systems are stated to be different areas, which may be present within the same room. But in lines 1283-1284 and 1288-1289, the word ‘area’ is used when ’room’ would appear to be intended.  It is also suggested to include a list of definitions and abbreviations in the next version of this guidance and define room and area to prevent from any confusion. It is suggested that it is not appropriate to conduct concurrent production of any products in the same ‘area’ (i.e., BSC/isolator) and that paragraph 1283– 1289 is deleted.**Proposed change (if any):**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).Delete the following sentences of the paragraph. It is also suggested to include a list of definitions and abbreviations in the next version of this guidance and define room and area to prevent from any confusion.  |  |
| 1280-1282 |  | If the batches or products are completely closed and physically separated, the possible risks are evaluated and appropriate measures to avoid mix-ups of materials are implemented, we consider that simultaneous incubation/storage of replication competent vectors/products based on them should be acceptable. To ask for individual equipments (incubators, ultra-freezers, etc,) might be impossible to implement in small GMP facilities.**Proposed change (if any):**Delete the sentence. |  |
| 1283-1289 |  | In line 1267/1268, closed systems are stated to be different areas, which may be present within the same room. But in lines 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’ (i.e., BSC/isolator) and that paragraph 1283 – 1289 is deleted.**Proposed change (if any):** Eliminate the sentence. |  |
| 1326-1328 |  | To reduce discussions in regard to handling of filters in different steps (sterilization, bioburden reduction,…) this sentence should be adapted.**Proposed change (if any):** The integrity of sterilised filters (validated sterilization procedure) should be verified before use and should also be confirmed after use by an appropriate method (e.g. bubble point, diffusive flow or pressure hold test).” |  |
| 1331 |  | It should be clearer defined which are the requirements for the different aseptic process validation focus: Operator – Room – Process Validation.  |  |
| 1346-1352 |  | The necessary Growth Promotion Test should be mentioned.**Proposed change (if any):**In line 1348: Via the growth promotion test the suitability of the media used for the individual media fills needs to be proven. |  |
| 1353-1354 |  | It should be clearer defined which are the requirements for the different aseptic process validation focus: Operator – Room – Process Validation. **Proposed change (if any):**Process simulation tests for the entire production process should be performed as initial validation with three consecutive runs. |  |
| 1355-1364 |  | Applying the standard frequency of process simulations for parenteral medicinal products to ATMPs is not sound logic. The risk associated with filling a single or small number of containers with an ATMP for an individual patient is different to that of filling thousands of doses of a medicinal product for multiple patients. 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 (on a case-by-case basis). This should not be a defined timeframe as it depends on different factors, including batch-size, comparability of aseptic processing steps within several ATMPs.**Proposed change (if any):**It is generally expected that the aseptic process validation is run every six months, as well as when there is any significant change to the aseptic process (e.g. 1356 modification of HVAC system, equipment, etc). A reduced frequency may be justified based on an risk-assessment covering the qualification of operators, aseptic validation of the process and the rooms.A reduced frequency is not acceptable when the product 1363 should be administered to the patient prior to having the results of the sterility tests. |  |
| 1381-1382 |  | **Proposed change (if any):** Where ionizing radiation is used to reduce bioburden and to sterilize the final product of the ATMP, Annex 12 to EudraLex, Volume 4, should be consulted for further guidance. |  |
| 1420-1424 |  | Reprocessing should be foreseen, described and authorised at the level of the authorisation dossier (CTA or MAA).That although authorised reprocessing should remain exceptional as it is a signal that something is going wrong with the process.**Proposed change (if any): Suggested text is underlined**Delete lines 1420 to 1424.Add: “Within the Annual Product Review the reprocessed batches need to be documented and an assessment needs to be done showing that the standard process is still valid.” |  |
| 1440-1441 |  | The point regarding validation of the computerized system(s) is well taken and relevant in the context of running production operations under "validated conditions". However, this sentence is relatively short, in contrast with the previous item on qualification of clean rooms for which there are norms or guidance to be followed. Validation of computerized systems is not that obvious. This generic and high level wording potentially opens the possibility for divergent interpretation between inspectors and manufacturers on the level of computer validation achieved and whether it is "proportionate to the impact…" **Proposed change (if any):**It is suggested to provide additional guidance on computer qualification and validation and/or add examples. |  |
| 1449-1460 |  | Aseptic process validation (APV) and equipment (re-) qualification should be clearly separated in this paragraph. Reference to Section 4.2.2. (Aseptic Environment) is suggested. **Proposed change (if any):**1) Separate sub-section on APV, apart from (re-) qualification of premises and equipment. 2) Add reference to Section 4.2.2. (Aseptic Environment).  |  |
| 1459-1460 |  | It should be distinguished between class A clean rooms and other classes A areas (BSC, isolator). It should be included that for BSCs a full re-qualification (all issues according to DIN EN 12469) should be performed only every 12 months and not every 6 months. The manufacturers of BSC’s recommend the procedure according to DIN EN 12469 once per year. Additional wording on BSC re-qualification is suggested. **Proposed change (if any): Suggested text is underlined**“In general, for clean rooms of class A… while for biological safety cabinets (BSC), B, C, and D grades….” |  |
| 1464-1468 |  | It should be made clear that the specifications for premises and equipment should indeed be defined by the manufacturer but this can only be done based on the set of specifications and product/process profile as defined in the authorisation dossier and obviously the "user specifications" set for premises and equipment should also be compatible with the intended process and quality profile to be operated in the premises.**Proposed change (if any): Suggested text is underlined**Line 1465 “The user requirement specifications should ensure……. linked to the manufacturing processes, as defined in the MAA**,** are….”  |  |
| 1547 |  | Not only the total number of batches manufactured but in addition a time frame should be added. The use of cleaning verification for investigational ATMPs should not be restricted to volumes of production less than three batches. Especially since no time frame is provided within the batches should be produced. The cleaning verification approach should be justified by the manufacturer. **Proposed change (if any): Suggested text is underlined**Line 1547:“For investigational ATMPs, cleaning verification is acceptable. In such cases…..”  |  |
| 1551-1557 |  | On the point of "process validation" there is a need to clarify, at the very beginning of chapter 10.3 that the process validation discussed here concerns the process, as it will be carried out on the GMP declared premises and equipment after the tech transfer has been done from the pilot lab to the "commercial manufacturing site". As such chapter 10.3 does not deal with the process validation, requested in section 3.2.S.2.5/3.2.P.3.5 of the CTD to be provided in an authorisation dossier. The objective of the process validation described here should be to demonstrate that the manufacturing process is capable to produce, in a reproducible manner, the final product defined in the MAA using the process described and validated also in the MAA. The validation described here is more an operational qualification and verification of the process, at the intended scale and site, than *stricto sensu* a process validation.**Proposed change (if any):** 1) It is suggested to extend this Section and add some wording around the objective of process validation: to demonstrate that the manufacturing process is capable to produce, in a reproducible/consistent manner, the final product defined in the MAA using the process described and validated in the MAA.2) Although the technical transfer of testing methods is specifically addressed in Section 12.3, there is no text currently regarding the technical transfer of manufacture to the commercial manufacturing site. It is suggested that this is addressed as part of the section on process validation. |  |
| 1575- 1580 |  | This sub-section states that three consecutive batches manufactured under routine conditions constitute a validation of the process. However, an alternative number of batches may be justified taking many factors into account. A few of these factors are summarized here. However, the list is not exhaustive and the approach to be taken by the applicant has to be justified in the MAA on a case-by-case basis. This is clearly described in the EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014). (http://www.ema.europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2016/04/WC500205447.pdf**Proposed change (if any): Suggested text is underlined** “It is generally accepted that the approach taken on validation of the manufacturing process, including the number of consecutive batches manufactured under routine conditions (i.e., being three, less than three, or more than three consecutive batches), is justified in the authorisation application (see EMA Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission (EMA/CHMP/BWP/187338/2014). (<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/04/WC500205447.pd>) for additional guidance). Factors to be taken into account include, but are not limited to, whether or not standard manufacturing methods are used, …”.  |  |
| 1587-1600 |  | The issue of validation with surrogate materials is well supported and welcome. However, and considering that the limitations evoked in this paragraph were also present at the time of the development (and validation) of the process at pilot scale, in preparation of the authorisation dossier, it is very likely that the "surrogate approach" has also been used at that stage. It is evident that experience gained during product development and scientific background should as well be taken into account to justify the recourse to surrogate materials already accepted/justified and authorised at the level of development in the CTA. These two paragraphs give the impression that the issue of "validation with surrogate material" is new and have never been experienced during the development phase. Taking advantage of experience gained during the development to help implementation in commercial GMP facilities is also part of the flexibility approach. **Proposed change (if any):** Add some wording around process verification/monitoring during product development with surrogate materials, as justified in the CTA.  |  |
| 1632-1644 |  | As for paragraph 10.3 (Process validation), there is here a risk of confusion on what is meant by "validation of test methods" and exactly using the same approach it would be important to specify that the "validation" requested here is essentially to document and demonstrate that, within the hands of the QC lab of the GMP facilities, the analytical methods (validation appropriate to the stage of development, for their intended purpose) are indeed operational and capable to operate with the analytical performances expected. As such this is not the validation of the method itself, but the operational qualification of the methods and technicians operating them.In this respect, lines 1637-1638 are clearly out of the scope of these GMP guidelines, as it is the responsibility of the authorisation process to ensure that, depending on the phase of development, the suitability of the analytical methods is sufficiently documented in the CTA/MAA. These method qualification/validation expectations should be addressed elsewhere, i.e., in ATMP pharmaceutical development guidances. **Proposed change (if any):** Delete lines 1637-1638.  |  |
| 1636 |  | The word “safety” may be misunderstood by some developers (i.e., pre-clinical safety testing), which is clearly not meant here. **Proposed change (if any): Suggested text is underlined** “Viral safety and microbial assays should be…”  |  |
| 1639 |  | The difference intended for potency assays versus 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).In addition, reference is made to the comments provided for lines 1632-1644 above. Method qualification/validation and phase based approach is out of scope for these GMP guidelines. The suitability of the potency assays should be sufficiently documented in the CTA/MAA.**Proposed change (if any): Suggested text is underlined**Delete lines 1639-1640. Alternatively, if expectations for potency assays are more formal than demonstration of suitability, then this needs to be clarified, e.g.:“In contrast to other assays, potency assays should be formally validated before Phase III clinical trials are started, unless otherwise justified”. |  |
| 1658-1659 |  | We consider very adequate the knowledge, training and experience requirements for QPs introduced in lines 1659-1663. Nevertheless, to maintain exactly the same qualification requirements provided for under article 49 of Directive 2001/83, it seems disproportionate for this type of products. As an example, it does not seem to make sense to maintain the necessity of having theoretical and practical studies on subjects like pharmacognosy.**Proposed change (if any):** To eliminate the sentence:” ~~In addition to having the qualification requirements provided for under Article 49 of Directive 1658 2001/83;”~~ |  |
| 1681 |  | Is there a certification of these testing units in a third country by an European authority necessary? Do the authorities have the applicable resources if yes? These points should be considered and addressed within the document. |  |
| 1817 |  | The preferred time point for such a notification should be mentioned (e.g. “prior to administration of the drug product”), considering the fact that in case of not cryopreserved, fresh ATMPs there is only a very limited time window due to the short shelf life. In addition to that 11.5 is not clearly worded in regard to the scope, is it applicable for both investigational ATMPs and authorised ATMPs? |  |
| 1862 |  | Retention of samples during clinical trials is an area which could be derogated to the competent authority in each MS and a specific sample retention proposal submitted for the investigational ATMP in the IMPD for approval. This would allow flexibility of application of the retention policy to reflect the individual nature of the ATMP under trial. This field is moving so rapidly that it is difficult to predict what products will be in development in the next 5 to 10 years so a flexible approach which is regulated by the competent authority conducting the GMP site inspections would be both effective and responsible.We agree that the question of Sample Retention might be easier with the new CT regulation. But will this regulation align with PIC/S?  |  |
| 1882-1888 |  | In echo with comment on lines 930-951 on Raw Materials (see comment on lines 1632-1644) it is not the responsibility of the manufacturer to assess whether a raw material (as well as any other materials) is "critical". This is done at the level of development and dossier and any recommendations or specific procedure will be laid down in the dossier, the manufacturer has then the responsibility to comply with. |  |
| 1886-1888 |  | We consider this requirement (to retain samples of critical raw materials) should be asked for “Authorised ATMP”. In the case of “Investigational ATMPs”, it might be more flexible.And also, the wording …“retained for two years after the batch release or one year after expiry date of the relevant batch, whichever is the longest” is difficult to realize due to the fact that in autologous setting raw materials are used very often for a bigger amount of individual patient batches over a longer period of time. We suggest that the time point for retention should be in accordance to shelf life of specific raw materials.**Proposed change (if any): Suggested text is underlined**To be added to line 1886: “In Authorised ATMPs samples of critical raw materials should be retained ….” |  |
| 1891 |  | It’s a reference sample and not a retention sample.**Proposed change (if any): Suggested text is underlined**We propose: “However, it is acknowledge that the storage of retention and reference samples may be challenging….” |  |
| 1900 |  | It’s a reference sample and not a retention sample.**Proposed change (if any): Suggested text is underlined**We propose: “The considerations regarding scarcity of starting materials apply –adapted as necessary- to the expectations of the storage of retention and reference samples of active substances ….” |  |
| 1912-1915 |  | For some autologous products, it is possible to keep a retention sample (e.g. one sample of starting materials can lead to produce one batch of a finished product filled in several identical containers such as vials). Where possible, the sample should be retained.**Proposed change (if any): Suggested text is underlined** “A retention sample is, however, not ~~expected~~ always possible in the case of autologous products or allogeneic products in a matched donor scenario as the unit produced with the patient’s tissues/cells constitutes should be administered to the patient.” |  |
| 1971 |  | In this paragraph on Stability Monitoring Plan (12.4), whereas the general principles are acceptable, it is strange not to find the same provisions and specific considerations as in paragraph 12.2. Indeed it is not reasonable to recommend any on-going stability program in an absolute way, not acknowledging the same limitations in terms of sample availability. Not in all cases it will be possible to use patient derived batches for stability programs, e.g. in case of small batch size in the autologous setting. Also, the potential use of material derived from healthy volunteers/ surrogate material should be mentioned. (The use of non-patient starting material needs to be well justified (i.e. through IMPD/MAA dossier).It is also proposed to add a cross reference to the limitations in the sampling strategy which should also be taken onboard when elaborating the stability monitoring program. |  |
| 2100-2101  |  | This example could be misleading by understanding that a third party (different from manufacturer and administration site) **that is GMP compliant** could perform reconstitution activities. “That is not GMP-compliant” should be deleted.**Proposed change (if any):** **Suggested text is underlined**It is suggested to modify the example as follows: “(i.e. it is not acceptable to have these steps outsourced to a third party).” |  |
| 2102-2115 |  | It is be pointed out that, when MA holder / clinical trial sponsor is different from ATMP manufacturer (e.g. when the manufacturing is done by a Contract Manufacturing Organisation (CMO)), the manufacturer (QP) is (only) responsible for checking that validation and documentation of the reconstitution process have been performed adequately, in accordance with the marketing/clinical trial authorisations and SmPC/IMPD ,whereas the MA holder/clinical trial sponsor are responsible for conducting the validation and preparing the documentation. This should be reflected in the document.**Proposed change (if any):** **Suggested text is underlined**It is suggested to modify the section 16.2 as follows:“The reconstitution process to be followed from the point of batch release to the moment of administration to the patient should be validated; i.e. through appropriate studies, it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent so that the product can be administered without negative impact on quality/safety/efficacy profile of the ATMP.The reconstitution process should be documented, including equipment to be used and requirements at the site of administration. The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product (e.g. when the reconstitution involves thawing, the rate of temperature change during thawing should be described).The manufacturer is responsible for checking that the validation and documentation of the reconstitution process have been performed adequately, in accordance with the marketing/clinical trial authorisations and SmPC/IMPD.Likewise, when the constitution requires the use of solvents and/or other materials these should be specified or, as appropriate, provided.” |  |
| 2110-2113 |  | The example could be misleading. Indeed, in some cases for cell thawing “the rate of temperature change during thawing” cannot be accurately defined (e.g. it is not always possible to define a rate of “+10°C/minute” but instead it would be “from -80°C to 0°C in 3 minutes”). Therefore, it would be clearer to ask for a detailed description of the thawing method to be applied for thawing (e.g. wait at room temperature, use of a water bath, use of a device, mentioning the duration/temperature…).**Proposed change (if any):** **Suggested text is underlined**It is suggested to reword the example as follows:“(*e.g.* when the reconstitution involves thawing, a detailed description of the thawing method should be included with temperature, waiting time, use of device…).” |  |
| 213017.2 Section |  | 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).It is acknowledged that clarification is 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. Nevertheless, the guideline should differentiate according to the type of manipulation. Whether the manipulation is not substantial, the obligations established in Directives 2004/23/EC and 2006/86/EC should be enough.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. |  |
| 2131 |  | A bracket is missing after “automated equipment”**Proposed change (if any):** “The user of the automated production system (hereafter referred to as “automated equipment”) (i.e. ATMP manufacturer)”. |  |
| 2200-2203 |  | There is a missing Section reference in Lines 2200-2201, which we suggest is Section 11.However, even with this reference, the sentence does not make sense as currently written and requires further clarification (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.**Proposed change (if any):** “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~~.  |  |
|  |  |  |  |

Please add more rows if needed.