ALLIANCE for Regenerative Medicine

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

Comments from:

Name of organisation or individual
Alliance for Regenerative Medicine (ARM) The Alliance for Regenerative Medicine (ARM) is a global, multi-stakeholder organization that promotes innovation, growth, and delivery of transformative treatments or cures for patients suffering from chronic, debilitating, and often life-threatening diseases, many of which are rare diseases. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 225+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community. Our aim is to connect all parts of the innovation lifecycle to address the unmet needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org. The consultation document has raised significant interest from ARM members. The current document is based on the detailed contribution from more than 10 member organizations and many more have reviewed and endorsed its content. Most of the contributing organizations are small- and medium-size enterprises (SMEs) dedicated to the development of ATMPs but we also received contributions from bigger companies with an interest in ATMP development, non-profit organisations or institutions, contract organisations involved in manufacturing ATMPs or starting materials for ATMPs, and other stakeholders.

1. General comments

General comments	
Welcoming the initiative	The Alliance for Regenerative Medicine (ARM) welcomes the stakeholder's consultation and wishes to thank the European Commission for the initiative it has taken to seek relevant information to help develop this document. In particular we greatly appreciate the willingness of the Commission, as can be seen by the questions raised in the document, to seek advice on whether greater flexibility could be applied without compromising the quality and safety of ATMPs and whether the requirements are well-adapted to the specific characteristics of ATMPs. We indeed believe that these two aspects, enhanced flexibility and specific adaptations of requirements to ATMPs, are key to supporting and fostering the development of these highly innovative medicinal products.
Incorporation of GMP for ATMP in the "The rules governing medicinal products in the European Union"	While not explicitly mentioned in the consultation document, we understand the Commission plans to publish the GMP requirements for ATMPs in a separate, stand-alone document, rather than to integrate it in the EudraLex Volume 4 of the "The rules governing medicinal products in the European Union". This differs from the usual approach related to specific products for which requirements are addressed as annexes to the core GMP referential in Volume 4. The majority of our respondents have marked a strong preference for an integration of the GMP requirements in a dedicated annex of EudraLex Volume 4 rather than as a stand-alone document, based on the following considerations: 1. *Lack of completeness* Many key GMP aspects, for example QA release, expiry dating, biocompatibility testing, vendor audits for contract manufacturing, etc., are missing in the consultation document. Since many hospital/university based groups and SMEs developing ATMPs may be relatively inexperienced in GMP and licensing requirements, we believe this will cause confusion and may lead to disparate practices. To avoid this, all these additional elements, which are currently part of Volume 4, would have to be added if the GMP guide is presented as a stand-alone document, resulting in an unnecessary duplication of work. 2. *Risk of deviations and different standards for ATMPs and other medicinal products* As many aspects of GMP are not specific to ATMPs, having 2 sets of reference guides for ATMP and non-ATMP products would invite potential disparities between the two and could cause some difficulties for companies and for Competent Authorities at time of inspection. A separate guidance would prove challenging for developers with diverse portfolios. As a result, we recommend that GMP for ATMPs be incorporated into an Annex of Volume 4, similar to what was done for the

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	blood derived products in Annex 14, for instance. The text should focus only on the GMP elements that need adaptations to ATMPs and should cross-reference the core GMP guide where applicable, i.e., where no specific adaptation is required. This approach would allow focusing on the singularities of ATMPs, leaving untouched the requirements that are common to all medicinal products for human use. Further to this way of thinking, some members also suggested that separate documents (as separate annexes in Volume 4) be made for Cell Based Medicinal Products (CBMP) and Gene Therapy Medicinal Products (GTMP) as the points to take into consideration are clearly distinct between the two types of products, and the GMP implementation is likely to differ considering the nature of each type of product. However perhaps this could be covered as separate sections in a distinct annex. It is recommended the ongoing revision of Annex 1 in Volume 4 (Manufacture of Sterile Medicinal Products) and the current Annex 2 (Manufacture of Biological active substance and Medicinal products for Human Use) are considered in the drafting of this guidance. If the proposed guidance is a standalone document, separate from Volume 4, it is unclear how medicines inspectors will inspect, this is particularly the case for companies who may produce ATMP and non-ATMP medicinal products. Consequently, there is a potential for disparity between inspections in member states. To prevent such uncertainty we request that the guidance document is approved by the Inspectors Working Group prior to finalisation. Please note that the specific comments in the text below are made on the premises that this document would be stand-alone. Many of these comments would not be relevant if, as we recommend, the GMP for ATMPs was defined as an annex to volume 4, focusing only on the specific aspects for ATMPs and cross-referring to other sections in Volume 4 for other, undifferentiated, aspects of GMP.
Applicability / scope	The overarching objective of GMP requirements is to ensure product quality and thereby the safety of patients who will receive medicinal products, whether in clinical trials or in commercialisation stages. It should therefore be applicable to all ATMP manufacturers irrespective of the location where these are made. In that respect we believe there is some inconsistency in the approach taken by the Commission for this consultation. Indeed on the Commission's website, it is stated that "**All** stakeholders involved in the development, manufacture and/or commercialisation of advanced therapy medicinal products" are addressed. However in the introduction of the document, hospitals and ATMPs manufacturers are clearly excluded from the scope of the consultation document (lines 69-74), even though it is recognized that ATMPs are also often developed in an academic or hospital setting (lines 118-119). Hospitals and academic settings are major stakeholders and should be consulted. Whilst we clearly acknowledge the greater flexibility required for manufacturing ATMPs in the early development

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	stages (see our comments below), it is difficult to understand why hospitals and academic settings engaged in the manufacturing of ATMPs would be exempted from applying the same GMP principles which aim to protect patient safety.
"Commercial ATMPs" versus "Investigational ATMPs"	Many of our members have requested additional guidance on the differential requirements for 'investigational ATMPs' and 'commercial ATMPs'. Expectations and requirements should differ depending on stage of development and the specific characteristics of the product (such as autologous versus allogeneic for instance). Applying a risk analysis based on the product characteristics and the potential benefit for the patient, more flexibility should be allowed in early stages of development, especially the early product development stages. A risk based approach is common for all products as they progress through the phases of clinical trial; the clinical trial regulation 536/2014 states that "*Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and their reliability and robustness of clinical data generated in the clinical trials ('good manufacturing practice')*." Even so, the regulation foresees "*In some specific cases, it should be possible to allow deviations from those rules in order to facilitate the conduct of clinical trials*." It would be important to ensure that a GMP guideline for ATMP that allows for flexibility at the investigational stages would not create misalignment with the new CT regulation. The risk specific nature which can be applied to ATMP is in relation to the information included in the MAA dossier (2001/83/EC Annex 1 Part IV). It is recommended that what developers would find extremely helpful in the proposed guidance would be 1) examples which act to demonstrate how a risk based approach can be employed during product development and trial and 2) how information for inclusion in MAA can be tailored based on a risk assessment.
Additional characteristics of ATMPs or information to be considered	Some specific characteristics of ATMPs such as the particulate inspection or release assays which are unique to ATMPs or other provisions such as the legal precautions for biosafety, environmental protection and work safety are missing and should be considered for incorporation in the document. Additional guidance based on the type of ATMP would also be welcome. The document in its current version focuses mainly on starting materials, but lacks clear guidance on other raw materials that may also have a critical influence on the safety and quality of the final cell product. Reference to the newly released EDQM monograph and PAS 157 on Raw materials is made.

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Global harmonisation and consistency with other documents	Convergence on GMP requirements with other international regions is important to avoid difficulties in mutual recognition schemes and unnecessary delays in commercialising therapeutics. Therefore convergence, wherever possible, with the GMP requirements in the US and other regions of the world should be considered desirable. As an example FDA requires data retention for 10 years plus the product shelf life, whilst this document requires 30 years after the expiry date of the product. The draft WHO guidance needs to be considered to ensure consistency and harmonisation when applicable, as well as the recently published second edition of the EDQM guide to the quality and safety of tissues of cells for human application. In addition, it should be in line with other documents that are currently revised, such as Ph. Eur. 5.2.12.
GMO requirements	Several ARM members have highlighted the difficulties to comply with the GMO/GMM related regulations, such as the Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms when ATMPs fall under the definition of GMO/GMM. These rules apply to transgenic food and animals as well as to medicinal products. According to these Directives, appropriate containment and other protective measures need to be established and maintained in facilities where any GMO/GMMs are handled. Experience from our member organizations shows that applications for use of GMO/GMM medicinal products in clinical trials are complex and lengthy. Different national competent authorities take extremely different approaches or different decisions; for example there is disparity in the interpretation of whether a product is being used under deliberate release or contained used. In addition, there is wide variability in the application processes, timelines and the documentation required to support the application. Whilst these considerations go beyond the scope of this document, we believe that a specific section outlining GMP requirements for the safe handling and containment of GMOs depending on the type of vector used, based on the route of administration (in vivo vs ex vivo), etc. would be helpful in fostering some level of harmonisation across member states.
Responsibilities of the ATMP manufacturer	We believe it is important to clearly delineate responsibilities of ATMP manufacturers from other stakeholders upstream and downstream to the actual manufacturing steps: - vis-a-vis blood, cells and tissues establishments who procure starting materials for ATMP manufacturers: The document mentions that "Blood establishments and tissue establishments authorised and supervised under Directive 2002/98/EC or Directive 2004/23/EC do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing according" (ref. Lines 466-469). It is also recognized that these establishments operate to the Good Principle requirements as set up in the respective Directives do and fulfil the quality and documentation requirements of accreditation schemes such as JACIE. As the quality of the starting materials is critical to the

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	quality of the final ATMP, the responsibility of the manufacturer, the QP in particular for the final quality and safety of the product and the possibility of audits of these establishments by the manufacturer should be further clarified. - vis-a-vis healthcare professionals/users who may be involved in the handling, preparation, reconstitution, use of the product prior to administration. There is unanimous agreement among our members that reconstitution prior to administration to the patient should not be regarded as a manufacturing step and should not have to be carried out under GMP requirements. It is proposed that any manipulation required prior to administration, including for instance the washing of cells for cryopreserved ATMP should be regarded in the same way and would fall under the responsibility of the healthcare professional/user involved in the handling of the product before administration. Manufacturer's responsibility would be limited to the qualification / validation of these steps and the transmission of detailed information to the users.
Format	Generally it would be easier to follow the plan of the current GMP guide structure, i.e., using the same headers and with information provided in the same order.
Wording	In its current version, the guide is closer to a guideline than a binding GMP document. While we understand that the purpose may be to allow for more flexibility, it often leads to potentially confusing elements. Whilst we agree the possibility to allow for more flexibility based on the stage of development, nature of the product and risk analysis should be allowed and guidance should provide guidance on the conditions to follow and the type of supportive elements (e.g., gap analysis between the proposed approach and the recommended GMP framework, risk assessment of gaps identified and additional measures taken to mitigate the risks). See comment above on the distinction between "commercial" and "investigational" ATMPs. We have also found that the terms "phases" and "stages" are used interchangeably. We recommend choosing one throughout the document. Finally adding definitions in a dedicated section would be helpful.
Answers to questions in the document	Please note that the answers to questions provided below under 'specific comments on text' reflect the different views from our members and may therefore provide different answers based on the large variety of experiences and activities of our members.

General comments	
Process and next steps	The intrinsic characteristics of many ATMPs pose specific challenges for the manufacturers as well as for health authorities. We appreciate the special mechanisms available for ATMP manufacturers to seek more frequent and focused guidance from EMA. We recommend the guidance document developed in consultation with and endorsed by the Inspectors Working Group. Finally, whether this document will be issued as a stand-alone or whether it will be issued as an annex to volume 4, significant adaptations would be required: it will have to be significantly expanded if it is a stand-alone; if it is issued as an annex to volume 4, the parts that are not specific to ATMP should be removed and a cross-reference made to other existing sections in volume 4. We urge a new public consultation when the draft Guideline on good manufacturing practice specific to ATMPs will be first released. In addition, we would also welcome a focused meeting, with the participation of the Inspectors Working Group, to have an opportunity for dialogue on some of the key aspects of GMP for ATMPs to facilitate implementation by all ATMP manufacturers and ensure patient safety.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
75 – Questions 1 & 2	All developers/manufacturers of cell based products should employ quality risk management (QRM) techniques (implementing ICHQ9) as an integral component of their pharmaceutical quality systems (PQS). QRM is a systematic process for the identification, evaluation, and control of risks to the quality of the cell-based product across its product lifecycle. Employing QRM principles early in product development can identify areas of risk that can be addressed before they are incorporated into the manufacturing process and affect the safety and efficacy of the product. Continuous employment of QRM can pre-empt risks. The level of effort, formality, and documentation of the risk management process should be *commensurate with the level of risk*, fact-based, science-based and linked to patient protection. Some benefits of the proper use of QRM techniques include: - can improve safety and efficacy of products by assessing patient risks, determining design space boundaries, or ranking quality attributes. -can establish and maintain a state of control by using risk management to drive process control. -can facilitate continual improvement by prioritising opportunities for improvement. It is however recommended that more specific guidance and recommendation be needed to avoid confusion and misuse. For this, minimum GMP expectation should be described, and where for specific reasons some of the GMP requirements are not achievable, then a risk assessment should be performed to support the proposed approach with additional measure(s). Examples: • By default under GMP for aseptic processes an A grade with a background of B grade is the requirement. If this cannot be fulfilled early in development, appropriate measures that may include additional environmental testing or measures taken in case of contamination alerts, etc., could be proposed to justify a A into C grade background. • By default retention samples sufficient to repeat release testing should be maintained. In the case of autologous

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	ATMPs with limited sample availability, a risk assessment around the absence of retained samples should be performed along with justification for their absence. This could be considered for autologous CBMPs but not for most viral vector for GTPs, for example (hence the need of specific text for each product type). • Meeting the requirements of sterility as per the Eur. Ph. (sample volumes, number of retains, etc.) is not always possible for gene modified cell therapy products because of limited starting material, the impact of donor variability manufacturing, and clinical need. See also the general comments above.
75 – Question 3	The question is unclear as to whether the EC is asking whether Directive 2004/23/EC be used alone or whether the Directive be replaced by the JACIE accreditation system or that additional GMP be established for the tissue collection practices. Directive 2004/23/EC does not require standards equivalent to GMP. The Directive reads more as good "tissue" handling practices and does not speak to specific requirements that would support or ensure safety and efficacy of the product if the tissues are manipulated in any way. This Directive is not explicit enough as would be expected for GMPs during late-phase clinical or commercial manufacturing. The legal status of accreditation and the legal ability of JACIE to enforce its regulations and guidelines would need to be explicitly clarified in order to assess the adequacy of using accreditation to supplement GMP expectations. The JACIE accreditation system, unlike EudraLex Volume 4 is not a recognized requirement for the manufacture of human medicinal products and therefore Medicine Inspectors would not inspect against this standard. In addition, the expectation of the applicability of GMP to starting materials should also be clarified. JACIE or equivalent could be recognized as the quality standard for cell procurement since it meets many of the underlying control principles of GMP even though its standards are not equivalent to GMP.

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	Since cell procurement results in starting material for an ATMP, and since the further manufacturing of the ATMP is covered by GMP, the question of GMP applicability to starting materials is important to resolve. If the decision is that GMP are not applicable for cellular starting materials, JACIE standards may be sufficient to assure starting material product quality, recognizing the need for flexibility of this approach. For commercial products, JACIE accreditation, in conjunction with sponsor qualification of procurement sites, can provide additional assurance that adequate controls are in place regarding the desired quality of the starting material, the traceability of the cells, training of personnel, adequacy of premises and documentation system etc. are met. Where possible we recommend that the EC take into consideration the guidelines of tissue banks around the world to have consistent global standards for industry. The answer to this question should be clarified in the GMP document, together with the question of the responsibility for the biological starting material.
82	Proposed change: After "trained" add "…in all aspects including technical and quality systems management".
99-101	Comment: Process monitoring is a critical control strategy due to the inherent variability of starting living materials. Proposed change: "The manufacturing requirements (e.g. specifications, manufacturing process, **process monitoring**, controls, etc) foreseen in the marketing authorisation or clinical trials authorisation should always be adhered to".

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102-127	Comment: it would be useful to add in section 2.1. specific reference to the existing Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products (EMA/CAT/CPWP/686637/2011).
105-106	Comment: We suggest adding text in conjunction with recognition of variability. Proposed change: add "Tighter controls on equipment, materials, etc., should therefore be employed and expected to minimise risk wherever possible."
107	Comment: one example is not clear enough, more complex manipulations should also be cited. Proposed change: change text in brackets to: "(e.g. cultivation of cells, manipulations altering the function of the cells)".
110-114	Comment: Typographical mistake Proposed change: add "to" after "comparison".
110-127	Comment: This section seems to indicate that flexibility means less GMP diligence. All aspects should be risk-based and may even mean more controls. Adherence to ICH Q9 should apply to ensure any allowed flexibility is fully thought through. While the point is clear that flexibility is warranted for early phases of clinical studies, it would be helpful to be clearer with respect to what flexibility would be allowed. Even if the ATMP manufacture is performed in an academic or hospital setting, basic controls on the environment and on personnel qualification and performance are expected. We suggest that the flexibility be tied to product knowledge and re-emphasize that product "safety" from a microbial

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	content or an adventitious agent standpoint should still be ensured. Specific reference to quality risk management and its principles as currently stated in chapter 1 in Part I, of EudraLex volume 4 should be made and could advantageously replace the current text in lines 115-122. Examples of the processes and applications of quality risk management can be found inter alia in ICH Q9 which is reproduced in Part III of the Guide. The risk management (1.13) should account the need for fail safe processes as potentially there is no chance for rework or repetition.
118-119	Proposed change: "operating under quality systems different to those…" Change the word "different" to "lesser than in pharma/biotech".
121	Comment: "for early phases of clinical trials": please be more specific. Proposed change: state Phase I only or Phase I, II and III.
120-122	Comment: It would be useful to include an additional level of detail regarding the application of the risk-based approach in the Guideline. Proposed change: provide some examples such as the following: 1. Potency assay is usually not developed at early development stage of ATMPs and should be considered as an aspirational goal but not a requirement for clinical batch release and stability testing, especially for clinical materials used for early phase studies (e.g., Phase 1 and 2). Dosing based on quantity (such as viable cell count) should be permitted for early phase clinical studies.

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	2. Due to the cellular nature of many ATMPs, it is not feasible to perform a compendial particulate matter test for ATMP batch release. It should be acceptable to limit the particulate matter test to foreign visible particles if there are alternative measures in place to control the level of particulate matter in the drug products. Such alternative measures may include (1) control the input of particles from the materials and equipment used in the ATMP manufacturing, and (2) perform simulated manufacturing runs (without cells) to validate and demonstrate the capability of the manufacturing process to produce low particle products.
123-125	Comment: As the experience of many of the manufacturers of the first-in-human studies is varied, the assumption that a majority of manufacturers have the knowledge to insert an example of their own risks which would require additional measures may not be correct. Many of these manufacturers of early trials have limited knowledge regarding requirements to with regard to GMP. Proposed Change: Provide an example of such 'specific risks' upon which 'additional measures' should be taken to illustrate the statement.
127	Comment: Explicitly allow changes to the control strategy based on new information. Proposed change: add the following sentence "New information obtained during development may alter the types of risk and risk levels such that in consideration of this new information, changes to the control strategy (analytical method update, addition or exchange) may be justified."
127	Proposed change: "the ATMP manufacturer should consider<u>, document, mitigate and justify</u> all the potential risks."

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128 – Question 4	The requirements as laid down in section 3 seem to be standard and probably do not need to be restated specifically for ATMPs. A reference to the existing requirements for GMP can be made here. The main area where section 3 could be further developed is the concept of cross-contamination (lines 147-151).
129-130	Comment: Adequate practical experience seems sufficient to define who can perform the intended operations. Proposed change: The ATMP manufacturer should have an adequate number of personnel with the adequate practical experience relevant to the intended operations.
138-139	Comment: The appropriate protective equipment for operations is open to interpretation. Additional guidance would be useful. Gowning requirements should be connected to the environmental controls necessary for the protection of the product. There should also be reference to training and qualification of operators gowning appropriately.
140-141	Comment: Check on health conditions is not allowed by Dutch law so this cannot be made mandatory by the guide. Proposed change: We propose deletion or rewording of this sentence.
141-143	Comment: The practice of performing a risk assessment on the risk of product contamination arising from employees should be suggested. The outcomes of the risk assessment should determine the risk reduction / mitigation activities to be implemented.

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144-146	Comments: It should be clarified that the health monitoring discussed in this sentence is intended to ensure employee safety rather than to protect the product. While we appreciate the qualifying phrase "proportional to risk" again recognizing the application of flexible standards, the statement is quite broad and perhaps specific guidance should be provided as to what pathogens personnel should be vaccinated against. For example, should <u>all</u> personnel receive the Hepatitis B vaccine?
147	Comments: Restrictions on the movement of personnel to minimise the risk of cross-contamination is mandatory. Facility flows should restrict people from becoming a source of contamination.
147-151	Comments: some facilities may prepare genetically modified cell therapies and "regular" cell therapies in the same production facility. We believe this should be possible and acceptable provided cross-contamination risks are assessed and adequately addressed. This section could be further developed with examples focused on the differences in expectation or acceptability (if any) for production of allogeneic cell therapies or autologous with respect to risk of cross-contamination due to personnel. This same comment is valid for lines 162-166 in the following section, but with respect to facility design and facility flows.
152-154	Comment: We do not understand what is the rationale or purpose of the sentence "Because of their essential role in the quality system, the person responsible for production, the person responsible for quality control and the Qualified Person ("QP") should be appointed by senior management." What is the definition of "senior management"? The personnel

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	responsible for the production, quality control and the QP should all have appropriate training and qualification. This expectation should be the same for all medicinal products and not unique to ATMPs. Proposed change: Change the sentence to "Because of their essential role in the quality system, the person responsible for production, the person responsible for quality control and the Qualified Person ("QP") should **have appropriate training and qualification and** be **duly** appointed ~~**by senior management**~~."
152-156	Comment: Quality should be a separate, independent, dedicated function, separated from medical staff and from the pressures of releasing a product based on a patient's disease state. What is important is the independence of the QP, not the appointment by senior management. Hospitals do not dedicate staff and they are not independent from patient outcomes. Proposed change: it should be made clear that the QP should not be the Principal Investigator. A medical doctor prescribing drugs should not be responsible for batch disposition.
157 – Question 5	Additional clarity would be useful to define where ATMP manufacturing begins and ends. Accreditation standards and other controls may be of value at the collection site (prior to receipt at the manufacturing facility) and at the clinical site (after distribution from the manufacturing site). The requirements laid down in Section 4 appear to have been overly adapted for the production of ATMPs. There are instances where the language used is subjective, is not open to interpretation and does not add any value. Such as the use of "carefully" in line 169 and "maximum" in line 174.

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	There a number of instances where the procedures requested are not feasible, have mixed concepts, or are unrealistic given the setting for example: lines 193-194 ask for decontamination of the heating, ventilation and air condition systems; lines 234-235 refer to " air vent filters (HVAC)" and state they should be "validated for their scheduled life span". It is assumed lines 234-235 are actually referring to vent filters on vessels not filters used within HVAC systems. As currently worded it could be misconstrued that the intent is to validate the life of filters in HVAC systems, which we believe is not the intent. A further example, is lines 237-238, it is agreed airlocks "should" be used to access cleanroom area, yet within certain settings such as hospital or academic it is not reasonable to expect or demand they be interlocked.
157 – Questions 6 & 7	An example of an additional flexibility that could be applied in connection with the requirements related to premises: Incubators which are dedicated for a product (with different lots/patients inside) are allowed in a cleanroom while different activities can take place in the same cleanroom. Section 4 repeats a lot of the routine expectations of the GMPs and could be simplified through a cross reference. The document would be enhanced by providing guidance on expectations for control levels when manufacturing different cell products (allogeneic vs. autologous) and including some examples or points for the manufacturer to consider as they design and control their facility. Section 4.2.2 requires full validation of premises for commercial production. There is no guidance on how much validation/qualification of premises is expected for early phase or for pivotal trials. We agree that additional flexibilities could be applied, while it is reasonable to expect some level of decontamination of facilities to support a multiproduct approach, requirements such as such as decontamination of the HVAC actually reduce

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	flexibility. With appropriate process controls such a need would be moot. Likewise procedural controls can be used for airlocks without the need for interlocking systems. The language used for premises should be more flexible as a number of initial (first in man) clinical trials, with regards to ATMPs, are generally initiated in hospital or academic settings and the premises at these sites most likely do meet the strict requirements detailed in this section. However, the use of more flexible language with regards to the premises in which the ATMP is manufactured in particular for first in man trials will not in any manner impede its quality. Ideally GMPs for investigational ATMPs should be structured more along the lines of those described for biological product as there is a great deal of similarity between the two. Only where there is specific knowledge or experience with an issue should greater details or expectations be called out. Some of what has been proposed throughout this document establishes higher and potentially different standards than in the other GMP documents. For examples the section on TSE/BSE goes beyond and above that which is specifically called for by current directives.
158-233	Comment: Relating to premises, as there are a spectrum of applications, the document would benefit from acknowledgement that level of controls will vary when comparing raw material used for a starting material, versus starting material used for a starting material or final drug product (e.g., recognizing that cell procurement will realize a different control environment than plasmids and likewise plasmids to vector manufacture).
159-161	Comment: how can the premises minimise the risk of errors? Errors might be an operator or procedure issue, not a premises issue. Proposed change: delete the words 'the risk of errors'. Add 'They should be designed to facilitate traceability of materials

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	throughout the facility".
168	Proposed change: Add, "The efficacy of the disinfectant should be demonstrated. An adequate degree of environmental monitoring should be implemented".
171-173	Comment: it might be relevant to include the need for monitoring key parameters as appropriate. Proposed change: Add, "Single pass HEPA-filtered air with continued monitoring should be implemented". Add, "Monitoring of these key parameters should be implemented".
187	Comments: Biosafety should apply and be mentioned at the beginning of the guideline. The suggestion was also made to focus on ISO standards rather than on laboratory terms such as "biosafety level 3 or 4". Proposed change: (i.e.**,** Biosafety ~~**I**~~**L**evel 3 or 4)
197-201	Comment: Consider that FDA CFR 211.101 requires "charge-in of components": Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information: (1) Component name or item code; (2) Receiving or control number;

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	(3) Weight or measure in new container; (4) Batch for which component was dispensed, including its product name, strength, and lot number
202	Comment: spelling error Proposed change: 'The ~~**laid out**~~ **layout** of the premises…'
205-207	Comments: The environmental classification is not described. In addition, there is no clear description of Air locks and pass through with pressure differential, interlocks and timing when doors can be open. Proposed change: add at the end of the sentence "A clean room with either C or D grade is sufficient for a completely closed manufacturing process" and consider adding above precisions in the text.
212-215	Comment: the sentence is confusing and it is questioned whether the author did not mean "If sterilization of the finished product is **not** possible, particular attention should be paid to the filling process"?
214-215	Comments: The word "qualified" should be used rather than "validated" (applicable to process or methods) when referring to premises. The use of the word "fully" is also questioned. Finally we believe the premises should be qualified for Phase 3 as well as for commercial production.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	Proposed change: "For **Phase 3 and** commercial production, the premises should be ~~**fully validated**~~ **appropriately qualified. The HVAC system/laminar air flow hoods should be qualified and premises monitored for investigational ATMPs**".
216-219	Comments: the should ensure alignment with the FDA aseptic manufacturing guidelines. The degree of environmental control and monitoring is not clearly described. Proposed Change: change to "Environmental monitoring programs shall address all production shifts and include scheduled monitoring based on a risk assessment. Monitoring shall include parameters common to the facility: air pressure differentials, temperature, relative humidity, viable and non-viable particulates, critical surfaces, equipment, and personnel (when appropriate). Periodical review of environmental data and trend analysis should be performed by manufacturers to verify the maintenance of effective environmental controls".
230-233	Comments: As microbial contamination arising from the production process is considered one of the major challenges related to cell-based products, the requirements for clean areas and processing in these areas should be addressed very early on during the clinical development: the safety from administration of contaminated products should be part of the safety evaluation in first-in-human (FIH) studies. Guidance is given for open processing (A/B). However, no guidance is given for fully closed processing. For example if the use of fully closed processing is used, or if "open steps" are performed in an isolator, it should be acceptable to locate these processes in such cases in a Grade C or D environment so long as the control of material and personnel flows and cleanliness are maintained. An appropriate risk analysis should take place to define the most appropriate manufacturing area, keeping in consideration the impact of using closed system.

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233 – Question 8	In general, we agree with the need for flexibility on clean room area background requirements for early phases of clinical trials. In cell-based products in which the starting material is usually a tissue or a blood product, sourced from an external institution, the requirement of a grade B surrounding for initial activities may not always be feasible. In addition, there may be activities such as solution preparations from powders, which may cause relatively high particle counts which will not comply with grade B requirements. Since the manufacturing process of cell based products is normally extended in time, it is our belief that in case of a contamination entering the product during the first stages of production, it will be discovered during later stages of the process, thus mitigating the risk to the final product. It is possible to prepare ATMPs in Grade A environment that is supplied by a Class C/D environment for early CBMP clinical development provided that : a) additional mitigation measures are in force, including extensive contamination monitoring, aseptic processing validation; and b) processes and technicians performing the procedure are qualified to produce an aseptic product FDA expectations for somatic cell GMP facilities should be acknowledged and taken into consideration by European regulatory authorities. While Grade A with Grade B background requirements are more stringent than the US requirement and are generally thought to be extreme, the allowance for relaxed requirements on background grade would more likely apply to academic centres in early phases. For cell and tissue-based therapies that are manipulated and manufactured under GMPs, the environment surrounding the

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	biological safety cabinet should be controlled and classified, usually as grade B clean room. This traditional design solution is Grade B (class 1000) cleanrooms with aseptic manipulations taking place within Grade A (class 100) biosafety cabinets. However, this has the disadvantage of high running costs, up to half the space being taken up with change rooms and airlocks, and only one product/therapy being processed at any one time within a suite. Higher therapy throughputs can be achieved with the same space and at lower running costs with lower grade cleanrooms containing 'closed' processes where aseptic manipulations take place within a Grade A glove box isolator. Fully closed processes similar to current small scale biopharma and/or the use of robotics can cope with higher throughput and to improve process robustness and reproducibility. Generally aseptic areas are not used for the entire manufacturing process. Rather their use should be dictated by the given state of the process and the potential risks to the process or product. For the final processing steps of the finished product aseptic techniques and facilities need to be considered where the finished product cannot be terminally sterilized. For commercial ATMPs inclusive of gene therapy products at the finished product stage it is reasonable to require that one comply with the aseptic processing guides. For first in man clinical product manufactured in either a hospital or academic setting it may not be possible to have full compliance especially as relates to Grade A within Grade B. Rather a more reasonable expectation is for Grade A within Grade C. Appropriate environmental controls need to be exercised and media qualifications need to demonstrate that product can be aseptically produced under such conditions. In earlier process steps the expectations for the environment and its controls should be the same as those applied for biologicals given the levels of overlap in terms of cell culture and purification.
240	Comment: it is not always clear what large scale manufacturing means and what requirements should be different for ATMPs.

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246	Comment: Some activities performed in clean rooms require drains to be installed. Proposed change: change to "Clean rooms should not have drains installed **where not necessary**".
248	Proposed change: Add "**Sealed, cleanable light fixtures should be used**".
252	Proposed change: Add "**Clear segregation should be considered between the various categories of materials,, such as starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled**".
260	Proposed change: Add "…unless controlled though a validated electronic system".
261	Proposed change: Add below this line "**Access should be controlled to all storage areas that contain materials that will be used in the production of investigational or commercial material**".
273 – Question 9	Section 5 does not seem to differ for ATMPs than for any other product types. The document might be simplified by cross-references to the already established GMP requirements. It is recommended to clarify that this should apply to all phases of development. An exception should be made for the statement on line 278 "equipment that comes in contact with product must not be

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	reactive, additive or absorptive". It is recommended that "must not" be changed to "should not". In early stages of product development it is generally not known if product is reactive, additive or absorptive. This information is typically assembled during the development process.
277-279	Comment: This paragraph requires clarification as in certain cases some equipment will on purpose be reactive with the cells (sort, activate, etc.). It is important to differentiate between inert and active equipment (meant to have an effect on the cells). Any equipment that contributes to the cell modification should in fact be CE marked. As an example, this will be the case for electroporator, cell selection system, etc. When a performance parameter of the equipment is implied, it should be CE marked.
274-298	Comment: Critical materials/equipment must meet documented requirements and specifications and when applicable the requirements of Council Directive 93/42/EC of 14 June 1993 concerning medical devices (2007/47/EC as amended). The equipment used should ensure that the procedure is done in a closed system (cell expansion). Application of biosafety rules should be mentioned.
285-286	Proposed change: "**Where appropriate, d~~D~~**istilled, deinised and**~~, where appropriate,~~** other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken".

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287	Comment: These systems must be validated and monitored according to compendium requirements.
291-293	Propose change: consider adding the following language: "For phase 3 and commercial manufacture, equipment should be qualified/validated. Procedures must be in place and changes must be managed by change control. Computers will be validated and password protected. Metrology may apply to equipment dedicated to operations".
299 – Question 10	In addition, guidance specific to ATMPs should include specific emphasis on the obligations of the hospital site to maintain full traceability of the product from receipt to administration would be advantageous because many clinical practitioners are not aware of this responsibility.
299 – Question 11	ATMP's manufactured for commercial use would follow the same principles regarding quality systems as more traditional pharmaceuticals. For example, a Quality Management system which includes CAPA, Change Control, Documentation Control, Batch Records, Excursion and Investigation Records etc. would still apply to ATMP's. There may be some difference in application, but the principles would be the same. Traceability will remain an important concern for ATMP products thus documentation should underscore this.
330	Proposed change: "It is ~~**recalled**~~ **understood** that changes into the manufacturing requirements..."

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332	Comment: "substantial modifications" need to be defined or at least be part of a frame. Some examples for investigational ATMPs would be useful.
335	Comment: We do not believe that a manufacturing order should be required as minimum documentation for early phase investigational products.
337-339	Comment: Regarding "Specifications of raw materials including: Instructions for sampling and testing as appropriate. For investigational ATMPs the manufacturer may rely on the CoA of the supplier if this is considered appropriate having due regard for the risks.": this should also apply to commercial ATMPs. Proposed change: delete "For investigational ATMPs".
342-344	Comment: It is not clear whether supply agreements with third party suppliers are mandatory or recommended from this sentence.
344	Proposed change: Add another bullet for "Infectious disease testing requirements".
352-353	Comment: It is not clear whether the term "substances coming into contact with the cells or tissues" refers also to disposables used in the process (i.e. tissue culture flasks, tubes, etc.). In our opinion it should not be required to have traceability for such materials.

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366	Comment: We would recommend to remove the rejection criteria and to keep only the release criteria. We support the acknowledgement that there will likely be characterisation results that are not available prior to product release. This is an important distinction for ATMPs and perhaps should be identified earlier in the document as it applies to more than just documentation. However a release strategy for characterisation result is not always possible to define for an investigational medicine. The ATMP manufacturer should issue certificates of analysis. Proposed changes: "Release ~~**and rejection**~~ criteria for raw and starting materials, intermediates, bulk and finished product, including release strategy for characterisation results that are not available prior to release**, as applicable**".
368-369	Comment: In allogeneic cell-based products, filling, packaging and labelling activities are performed immediately as part of the manufacturing process and therefore many times are not labelled individually per subject. Proposed change: we believe the following sentence should be deleted: "~~**Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial**~~."
373-374	Proposed change: Change to "Sufficient reconciliations should take place to ensure that the correct quantity of each product required has been accounted for ~~**at each stage of processing**~~".

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375-376	Comment: Rather than "thawing procedure", we recommend using the clinical / regulatory term commonly used, "Reconstitution". Instructions for product preparation prior to administration should be developed in detail and provided by the manufacturer during clinical development and is expected to be part of the Summary of Product Characteristics for approved medicinal products. See also answers to questions 22-24 below.
379	Comment: The word "significant" may be subject to interpretation. Proposed change: "Any ~~**significant**~~ deviations should be recorded and investigated, and appropriate corrective actions should be taken"
382-386	Comment: Requirements of the Annex 13 of EudraLex Volume 4 should be mentioned. When different manufacturing steps are carried out at different locations, it may be acceptable to limit records to the activities in the respective locations under the responsibility of a local QP but a comprehensive review of the manufacture steps against the product specifications should be ensured.
388-398	Comment: storage conditions and storage period upon receipt might be relevant information. A separate section for requirements of APH starting material to indicate traceability, testing, etc. Proposed change: consider adding the above-mentioned information.
394	Proposed change: "- ~~**manufacturer's**~~ **supplier's** batch or reference number"

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399-413	Comment: In the current phrasing it seems that the use of initials as identification is a requirement. We believe it should be allowed but not required.
411-412	Comment: Deviations should be investigated with impact to product assessed prior to disposition.
415	Comment: it might be relevant to keep all traceability records as auditable documents and not to include them in each batch processing record. Several batches of allogenic products might use same starting materials (cell bank) and same lots of biological raw materials (serum).
423	Comment: regarding (i) qualification or validation of processes and analytical methods, the question is whether this can be specified in more detail. We need to know at which stage of the investigational program this must be the case: Process validation from phase III onwards? Method validation from Phase III (IIb) onwards?
425	Proposed change: Add bullet points for CAPA and Change Control.
438-441	Comment: It is not clear whether the term "substances coming into contact with the cells or tissues" refers also to disposables used in the process (i.e. tissue culture flasks, tubes, etc.). Also, it is not clear what kind of traceability documentation is expected in case of raw materials not of biological source. In our opinion traceability documentation should be retained for a minimum of 30 years only for the starting material – the

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	source of the cells and the final product. A thirty year record retention requirement for any material coming into contact with cells would prove to be quite burdensome to manufacturers. The requirement for a 30-year document retention period in the ATMP Regulation arises from the requirements for donor record retention in 2004/23/EC and 2002/98/EC and these directives should be referenced for transparency. We believe that the 30 year retention policy is excessive but recognise that a formal revision of the blood and tissue directives and the ATMP Regulation would be necessary to address this requirement. Convergence with US and Japan requirements would be helpful (for instance, FDA requires data retention for 10 years plus the product shelf life) and should be considered if these Directives are to be revised.
438-441	Comment: it might be relevant to specify that keeping documents for 30 years applies for products delivered to patients. Proposed change: "For **all** cell-based products **delivered to patients**, data ensuring..."
442 – Response to Q13	Defining raw material and starting material would be very beneficial to the positions presented in the guidance. For clarity it should be broken down into 2 separate sections as challenges, expectations and requirements for each are different. We recommend more detailed information relating to the steps for which donation and procurements directives apply and the steps from which GMP should be applied. The Joint Accreditation Committee-ISCT (Europe) & EBMT (JACIE) provides certifications for starting materials which are not equivalent to GMP standards. Clarification is sought whether JACIE needs to be revised to higher standards or whether this is acceptable to regulatory authorities. See also response to question 3. Manufacturers of cell-based products must ensure that all components used in manufacturing are appropriately qualified.

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	For example, ancillary materials (AMs) not intended to be in the final formulation, such as cytokines and growth factors, but which affect cell growth, differentiation and proliferation or function of cells are critical raw materials. Variability in their quality can affect the quality of the final cell therapy. Potential lot-to-lot (or even vendor-vendor) variability in complex biological protein-based cytokines such as (post-translational modification) glycosylation/glycoform patterns may affect the final cell product, introducing variability. This would stress the importance of their qualification and assessment of AM quality attributes. In general the requirements laid down in Section 7 are well-adapted; however there are major inconsistencies in this section. The section points to the appropriate European Pharmacopoeia (Ph. Eur.) chapter for overall quality of the raw materials and to the appropriate directive for procurement and testing of human tissues. However for Transmissible Spongiform Encephalopathy ('TSE ") the section lays down the requirements. The overall quality of the staring and raw materials including "TSE" should be based on the Ph. Eur. general monographs and appropriate directives as these are legally binding. Hence requirements with regards to "TSE" should reference Ph. Eur. Chapter 5.2.8: Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.
443-445	Comment: The expectations for the sourcing of starting materials from hospital settings where GMPs may not be in place should be clarified (see above).
450-454	Comment: We believe this section should provide clearer guidance on raw materials that may have a similar critical influence on the safety and quality of the final cell product. Proposed change: "Where possible, raw materials used in the manufacturing of ATMPs should take into consideration the

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	Ph. Eur ***5.2.12.*** *general chapter on* ~~***qualification of***~~ *raw materials* ***for the production of*** *cell and gene* ~~***transfer***~~ ***therapy medicinal*** *product****s*** ~~***production***~~***, in particular with respect to the origin of raw materials and viral and microbial safety.*** The ATMP manufacturers should put in place appropriate measures to ensure that raw materials can be traced to their origin **and with respect to their manufacturing procedure** in order to facilitate recall of products if necessary".
455	Comment: typographical error. Proposed change: "The donation, procurement and testing of human tissues and cells ~~**of**~~ used as starting materials…"
458	Proposed change: "…appropriate steps to ensure the quality, safety and traceability thereof **at every phase**".
462-469	Comment: The expectation for donation, procurement or testing is critical to the safety and efficacy of the product. Inspectors for these types of establishments do not have product specifications for all types of starting materials. It is therefore necessary that manufacturers have assurances their products have been procured and tested appropriately to verify the quality of their product. The capabilities of the supplier should be confirmed in an audit by manufacturers. We thus believe that the last sentence should be removed. If maintained, references to the Directives in this sentence should be consistent (e.g. Directive 2004/23**/EC**) and a footnote consistently used. Proposed Change: "The ATMP manufacturer should verify compliance of the supplier'**s materials** with the specifications."

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466-469	Comment: The quality and safety requirements defined by Directive 2002/98 and 2004/23 are not equivalent to GMP and differences in approaches by national competent authorities may not be fully excluded. The Joint Accreditation Committee-ISCT (Europe) & EBMT (JACIE) provides certifications which are not equivalent to GMP standards. Clarification is sought whether JACIE needs to be revised to higher standards or whether this is acceptable to regulatory authorities. In addition it should be clarified whether a QP release is expected and required upon receipt of a starting materials from tissue or blood establishments.
474-476	Comment: We recommend clearer guidance on raw materials that may have a similar critical influence on the safety and quality of the final cell product. Proposed change: "The risk of contamination of starting and raw materials **of biological origin** during their passage along the supply chain must be assessed with particular emphasis on **viral and** microbial safety and Transmissible Spongiform Encephalopathy ("TSE")".
481-484	Proposed change: "For cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, it is particularly important to take appropriate measures to ensure the **safety and** quality of starting and raw materials".
485-488	Comment: in the vast majority of applications, sterilisation by heat will not be possible. It is important to stress that the sterilization process should be shown to be effective both in removing or reducing the contaminants and preserving the activity of the material (particularly for raw materials and excipients). As already stated in other parts of this document, the guidance should be based on an appropriate evaluation of the risks. All the techniques can be considered as effective when

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	appropriately applied and verified, and therefore should not be emphasised over another or exclusive. Where possible the choice of sterilization method follows the decision tree. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003520.pdf Proposed change: "Where sterilisation of starting materials and raw materials and excipients is required, ~~**it should be carried out where possible by heat**~~ **methods shall be used for inactivation of biological materials such as heat, irradiation, filtration or other appropriate methods**".
489-492	Comment: regarding the use of antibiotics, additional guidance is requested whether, if Penicillin type antibiotics are used, other products could be produced on the same line and whether the use and the type of antibiotic should be listed on the product label.
500	Comment: automated system should be allowed, such as those using bar codes.
513-514	Comment: This sentence is misleading. For starting materials following Directive 2004/23/EC the ATMP manufacturer cannot take over the responsibilities. For all other starting materials, standard GMP applies. See also annex 2 of EudraLex Volume 4.
515 – Question 14	There are a few instances where procedures in Section 8 requested may not be feasible and unnecessary for example line 545 where it requested that "the liquid nitrogen level be monitored".

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	Since many ATMPs are cell products, this section on cell banks and seed lots would need further development. It should however be recognized that the manufacture of cell banks is not always necessary for ATMPs. If the main focus of this section is for the generation of materials used in the production of ATMPs, that focus should be clarified. If the section is aimed at ATMPs that come from seed lots or cell banks, then there are additional important criteria and controls established to manage and monitor tissue banks that should be referenced and expanded upon. The term 'cell stock' and whether it is similar to 'cell bank' should be clarified and used consistently in the text. Cell bank safety testing and characterisation are important for lot-to-lot consistency and freedom from adventitious agents. The Master Cell Bank (MCB) and Working Cell Bank (WCB) should be minimally tested for identity, sterility, purity, viability and the presence of viruses or mycoplasma. Although not specifically intended to cover cell or tissue-based products, ICH Q5A, Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin, gives specific recommendations for testing cell banks for viral agents which are generally applicable. Additional virus testing may be needed depending on the prevalence of viral diseases endemic in the donor population. Cell bank characterisation should encompass additional assessments such as: growth kinetics and population doubling time, morphological assessment, percent confluence at passage, cell counts, viability, phenotypic expression of desired and undesired cell types, monitoring of unique biochemical markers, assessment of functional activity, gene and protein expression analysis, expression of immune histocompatibility antigens, molecular fingerprinting, chromosomal stability… In certain cases in Stem Cell Therapy, for example, cells are grown into an "intermediate cell stock" which is then further processed. We have seen cases where this Intermediate Cell Stock is considered as a cell bank. However due to the fact that the cell stock is not perennial, these intermediates should not be considered as a bank but rather as manufacturing intermediates to be tested and characterised as such. We have seen other cases where these cell stock intermediates were

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	considered Drug Substances despite the fact that they were significantly processed further. We would welcome some clarification on the terminology and expectations as they relate to these intermediate cell stocks.
519	Comment: Reference to the ICH cell bank guideline should be added.
538-543	Comment: Many more requirements apply to cell stocks than those listed here. See above in answer to question 14.
541-543	Comment: In the sentence "Cell stock changes should be addressed in the marketing authorisation and the conditions therein should be complied with", the term "cell stock changes" should include introduction of new cell bank(s) obtained from new donors. Proposed change: "Cell stock changes **and introduction of new cell banks(s) derived from new donors** should be addressed in the marketing authorisation and the conditions therein should be complied with."
554-558	Comment: We welcome this statement and believe it would be useful to mention that the lack of GMP compliance may also be addressed through risk assessment (e.g. lack of quality documentation). Including some examples of what constitutes "exceptional and justified cases" would be helpful. Proposed change: "In these cases, the lack of GMP compliance may require **risk assessment or** additional testing to ensure proper quality...".

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559 – Question 15	The requirements laid down in Section 9 appear to have been overly adapted for the production of ATMPs. It is suggested that this section have a preamble that indicates that the development of a product is phase dependent and procedures and quality controls will become more refined and detailed as development progresses. It is agreed that the production of ATMPs should follow appropriate and adequate controls for cleanliness, prevention of contamination and sterile operations. However a number of procedures detailed in this section tend to be over exacting and not necessary. For example: l) line 645 "manufacture of different viral gene therapy vectors in the same room is not acceptable". Manufacture of different viral vectors should be separated by space/time and appropriate controls and not by area. The overall goal is to prevent contamination yet allow for flexibility and more efficient and cost saving production. This does not require dedicated rooms. 2) lines 659-661 "If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, etc. to bioreactors should be used where possible." In-line filters should be used only where appropriate and feasible. It is not feasible to use in-line filters at each step and often other sterilizing techniques can be used effectively.
565-568	Comment: the wide variability in the characteristics of starting materials may justify deviations from instructions and procedures which may still be acceptable. However such deviations should be distinguished from deviations due to operational errors which should be appropriately documented and addressed by CAPA. Proposed change: "Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by the person responsible for manufacturing, with the involvement of the

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	person/department responsible for quality control when appropriate. **In addition, deviations due to operational errors should be addressed in the quality management system by corrective actions / preventive actions".**
570	Proposed change: "The effects of changes in the production (…) should be ~~**considered**~~ **justified and documented** prior to implementation".
582	Proposed change: "Checks**, including calibration checks,** should be carried out…".
590	Comment: GMP requirements include identity tests to be performed on all materials. Proposed change: "All incoming materials should be checked **and identity tests carried out** to ensure that the consignment corresponds to the order."
599-601	Comment: This requirement is not always feasible. We believe it should be deleted. Proposed change: delete this sentence.
618	Comment: The word "should" may mean a recommendation rather than a requirement. A material can be dedicated for a particular product, intermediate or a manufacturing step but not necessarily autologous.

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	Proposed change: Change the sentence to "Mix-ups of dedicated **and/or (**autologous**)** materials **must** ~~**should**~~ be prevented**, including associated samples and documentation**."
621-623	Comment: sterilisation of starting and raw materials has already been covered earlier in the document. Proposed change: "For ~~**non-sterile**~~ raw or starting materials, additional steps …".
624-627	Comment: we recommend further clarification of this sentence and the associated requirements.
628	Proposed change: "The manufacture of the active substances and finished products should be ~~**separated**~~ **segregated** from the manufacturing…".
630-639	Comment: Measures to prevent cross-contamination must be associated with robust and validated cleaning and environmental monitoring programs. Proposed change: appropriate wording should be added to clarify this.
639	Proposed change: "~~**Use of**~~ **Implementation of** single-use technologies.

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639	Proposed change: add a bullet "(v) Training".
645	Comment: We would welcome clarification on whether this requirement would apply when using single-use technologies and closed systems.
646	Proposed change: "Before any processing operation is started, line **clearance** steps should be taken…"
649	Comment: At the beginning of the development process a completed cleaning validation is difficult if not impossible to achieve; cleaning verification based on risk analysis should be acceptable. Proposed change: add the following sentence at the end of line 649: "**For first-in-human studies, a cleaning verification based on risk analysis is acceptable**".
649	Proposed change: "For cell-based products, cleaning validation between the manufacturing of different batches should be performed **as appropriate**".
660	Comment: in-line sterilisation of "regular" anti-foam is not possible. Proposed change: In-line sterilising filters for routine addition of gases, media, acids or alkalis, etc., to bioreactors should be used where possible. **If not possible appropriate measures should be implemented to handle and transfer**

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	aseptically pre-sterilised materials.
662	Proposed change: "Addition of materials or cultures ~~**to fermenters and other vessels**~~ **culture vessels** and sampling..."
665	Proposed change: "~~**Continuous**~~ **Appropriate** monitoring of some production processes (e.g. in bioreactors) may be necessary".
673	Proposed change:"… and sanitisation or sterilisation methods of ~~**columns**~~ **chromatography materials** should be defined".
Chapter 9.5	Comment: clarification is sought on whether primary packaging materials apply to medical devices regulations.
682-683	Comment: Extractables and leachables need to be considered, including any adhesive leaching through the bag. Container closure testing is required.
687-689	Comment: As acknowledged in other parts of this document, many cellular therapies must be released before final test results are available. Sufficient flexibility should be allowed such that quarantine requirements do not conflict with expedited release strategies. However this is not clear in the way the document is currently written. We would suggest the specific GMP guidance takes into consideration the notion of pre-release or "authorization for administration" of ATMP, such as in cases where the ATMP faces to a short shelf-life and cannot be fully released before administration. In such a case the final release is confirmed after patient

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	administration.
708- Questions 16 & 17	We believe the general principles laid down in Section 10 are well-adapted to ATMPs for both early and late stage development. It is especially reassuring that lines 711-713 are included which acknowledges that the manufacturing process for investigational ATMPs are not expected to be validated to the extent necessary for commercial ATMPs. We consider that validation should be performed according to the currently available guidelines, which already allow the use of supportive data when the number of batches is not sufficient, using a risk based approach. We recommend encouraging the use of as much supportive data as possible for ATMPs, when it is no possible to generate sufficient data on manufactured batches. In addition, it would be helpful to have the position of the regulators on the possibility to use model cells or surrogate systems for validation (such as declassified starting materials, similar cell lineage, when applicable). One of the key problems faced when dealing with cell-based product validation is the setting of relevant validation acceptance criteria and interpretation of results, given the variability of the starting material and DS/DP and the difficulties in comparing absolute values that may always differ due to intrinsic variability. It would be interesting to detail possible validation strategies that could be considered in order to allow for a better assessment of process reproducibility/consistency either by using an internal reference cell or considering process "efficiency" comparison rather than by solely comparing product absolute values (i.e., if a step is implemented to remove certain impurities, validation could be carried out by comparison of the % impurity removed for each validation run rather than the absolute impurity value). We strongly believe that the use of such approach will permit a better interpretation of the validation data, avoiding the difficult interpretation of variable absolute values.

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	An adaptive approach where the identification of surrogate markers reflecting critical quality attributes are continuously tested and assessed, either as part of the control strategy (analogous to PAT) or the release process, could be considered and used as an alternative to process validation. This is akin to stringent continued process verification applied to each batch and provides a much more robust assessment of the state of control of the process given the high variability of the starting material. This does not preclude the qualification of individual steps or "unit operations" to perform their intended function.
711	Comment: same comment as above on line 423. Additional clarification is sought on the extent of validation required for investigational ATMPs.
716	Proposed change: "Validation of aseptic processing should include a process simulation test using a culture medium (~~**media fill test**~~ **aseptic process validation**)"
722-724	Comments: We recommend indicating that a change control process should be employed. In addition, the wording in the second sentence could be improved as validation of changes in a manufacturing process that is potentially not yet validated sounds confusing. Furthermore, additional requirements regarding comparability of the manufacturing processes would be useful.
726	Comment: "substantial modifications" might require one definition or at least a frame.
753-774	Comment: The document provides good recommendations for how an ATMP from a third country is handled in the EU with respect to QP oversight and release. Similar to the comment in 382-386, consideration should be given to how the

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	information is consolidated and available to the QPs for a comprehensive review. In addition, guidance for how investigational ATMPs from a third country would be handled in the absence of a centralized system for clinical trial application approval would be helpful.
824-826	Comment: it would be useful to clarify what might be the minimum acceptable release criteria for investigational ATMPs.
839	Comment: it should be clearly stated that the QP cannot be the Principal Investigator or any other medical doctor prescribing the ATMP.
841	Comment: We welcome the language stating that the QP is not required to certify packaging and labelling activities performed at hospital. This adds helpful clarity to this part of the process.
865-869	Comment: Some ATMPs may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed. ATMPs product release may be carried out in two or more stages, before and after full analytical testing: a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the ATMPs under quarantine status to the clinical department. b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Qualified Person. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should finally

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	certify the product after all the test results are obtained. See also comments on lines 687-89.
883-885	Comment: Similar to lines 378-379, the term "significant deviation" raises concern since it is then open to interpretation what criteria are used to distinguish what constitutes a significant deviation. Some clarification and/or specific examples of what types of deviations rise to the level of being "significant"?
886 – Response to Q 19	Quality control test on an aseptic ATMP Drug product is expected to be tested on particles but this is impossible for ATMPs as they are, in most occasions, not clear solutions but cells in suspension. A visual control (according to European Pharmacopeia) cannot be performed when the solution is not clear. Considerations on these aspects should be added in this section, such as a statement that test particles should not be carried out on cell-based products. The QP needs to have the knowledge on ATMPs (at least similarly to the requirements laid down in the 2004/23/CE Dir.), and this should be stated as part of the GMP.
921	Comment: Additional details are needed in cases where it is not possible to retain samples (often for ethical reasons for autologous products, related to the limited amount of product available). In such cases, we foresee that mitigation measures would be difficult to implement, and we consider that the lack of sample should be acceptable if justified and documented and if development supports the fact that absence of retain samples or low amounts of retains samples was acceptable.

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942-943	Comment: it should be clarified to what exactly the retention period, the stability and the shelf life applies: the end-product ATMP or starting materials?
958	Comment: Additional language could be added to recognise that the establishment of reference materials is sometimes challenging for ATMPs.
980	Comment: Additional details on the handling of Out Of Specification (OOS) and the release of product with OOS would be welcome. Particularly for autologous products there may be specific situations where the product has to be infused even if tested OOS; the approach and measures to take in such cases should be discussed.
986	Comment: We believe that there should be trending for phase 3.
987	Comment: The technical transfer of testing methods does not appear to be specific to ATMPs and applies in fact to any products. Whether technical transfer of testing methods should be addressed in this document is questionable and if it will be addressed, then the equally important process transfer should also be addressed.
997-999	Comment: It would be useful to clarify whether validated conversion factors are acceptable between test methods.

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1000-1007	Comment: Stability monitoring program is relevant mainly for allogeneic products. It should be clarified whether and how this requirement should be addressed for autologous cell therapy products. Additional guidance on how stability monitoring programmes for autologous ATMPs have to be addressed would be particularly welcome. Most ATMPs are intended for use within a short time and the period of validity with regard to the biologic shelf-life, must be clearly stated. ATMPs having long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the QP. For each ATMP, feedback from the clinical staff on the biological characteristics should be received to ensure the stability of the process.
1007	Proposed change: After line 1007 add "**During CTA, complete stability data may not be available. Stability testing plan can be presented as rolling stability plan and reporting frequency should be defined**".
1008-1034	Comment: Requirements for outsourced activities as outlined in this section should exclude more clearly organisations showing compliance with Directive 2004/23/EC or 2002/98/EC. Microbiological laboratories carrying out certain tests on pathogenic organisms need to be included.
1014-1015	Comment: we believe it should be added that collection sites should fall under the requirement of requiring an assessment by the manufacturer.

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1027-1029	Comment: Additional clarification is sought on who is responsible for conducting comparability studies if there are approved changes in the process between the contract giver and the contract acceptor.
1054-1056	Comment: In cases where the ATMP was already administered, the process for notification of the Health Care Provider and the competent authority should be addressed both at clinical development and commercialisation stages.
1057-1060	Comment: see our general comment on 'GMO requirements' above.
1061 – Question 22	We agree that where reconstitution of the finished ATMP is required, the manufacture's responsibility is limited to the Qualification/Validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users. The manufacturer is responsible for the development of processes to be implemented at the infusion site upon receipt of the product, be it thawing and resuspension, or reconstitution or dilution. The detailed information and protocol should be provided to the users (e.g. requirements for the 'diluent'). In addition, the manufacturer is responsible for the establishment of the release criteria applicable to the reconstituted product if relevant (i.e., viability, cell count, visual control). The user will remain responsible to perform the release of the reconstituted product according to manufacturer specifications but also for the training and periodic evaluation of the personnel performing the reconstitution.

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	As the proper handling and administration during this step is equally important as all previous steps in the process (from procurement, through DP release and shipping), manufacturers should employ controls where possible (i.e., training certification, implantation manuals). The manufacturer should verify that the receiving hospital / pharmacy / user are capable of performing these tasks adequately, particularly with respect to the assurance of integrity and sterility of the final product dosed into the patient. This may include supplying detailed information on the technical requirements and how to fulfil them, as well as training (e.g., for a specific, complex reconstitution or application procedure). The term "validation" is not necessarily appropriate here. Added language on this topic would be helpful. The term "reconstitution" could also be changed into "handling, preparation and use". The definition of the "reconstitution" largely refers to EudraLex Vol IV (GMP), Annex XIII, Notes, 2nd note entitled "Manufacturing authorisation and reconstitution" which defines the inclusive list of manipulations of pharmaceuticals for which a manufacturing authorisation is NOT required. Any other manipulation do require a GMP-certified environment and a Qualified Person certification. From the time of EudraLex Vol IV (GMP) release, ATMPs emerged and experience showed that, in the vast majority of clinical indications, (cryo-)preservation of cell-based products is desirable to overcome the short shelf-life of fresh cells. Not only thawing but also washing and centrifugation steps are necessary to remove the cryoprotectant solution including DMSO and to reach adequate concentration for the finished product. Optimized removal of process-related impurities including residual amount of cryoprotectant solution positively impacts the safety for the patient. However, the removal of cryoprotectant by successive washing and centrifugation steps goes beyond the examples of "reconstitution" proposed in the present Consultation Document which are limited to "*dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes)*".

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	Today, CE-marked, automated closed systems (i) allow for cell separation based on continuous centrifugation during washing steps and (ii) assure traceability as well as efficiency, with the limited intervention of an operator. Examples exist showing (i) that these "reconstitution process" involving washing and centrifugation steps can be conducted safely and efficiently at the clinical site, following ATMP Manufacturer's Standard Operating Procedures and (ii) that closed systems can be extensively validated by the ATMP manufacturer during clinical development to reconstitute the product while preserving it from external contamination, maintaining the quality of the cells (release criteria maintenance) and removing the DMSO used for cryopreservation. In the case of cryopreserved ATMPs, the manufacturer would be responsible for the release of its product based on the complete results obtained from the full set of release testing performed on cells suspended in the cryopreservation solution that is the latest step where technically feasible before injection into the patient. Reconstitution process would be developed and validated by the ATMP manufacturer to reconstitute the product while preserving the product from external contamination, maintaining the quality of the cells (release criteria maintenance) and removing the DMSO used for cryopreservation. Users would be provided with sufficient information allowing them to perform reconstitution of the product safely and efficiently, in the best conditions allowing matching of patient's and operators' availabilities. Considering reconstitution out of the scope of the manufacturing authorization and, therefore, limiting manufacturer's responsibility to the validation of the process of reconstitution and to the transmission of detailed information about the process of reconstitution to the users is essential to reach "the objectives of free movement of those products within the Community and effective operation of the internal market" (cfr recital (5) of EU Reg. 1394/2007: "*Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector*"). Setting up dedicated GMP-compliant manufacturing facilities at or near every site where ATMPs shall be used to perform the thawing-washing steps and have a QP controlling these steps to certify the

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	quality attributes before release is not sustainable industrially and financially and prevents patients from accessing the product.
1061 – Question 23	In line with our answer on question 22, we agree that reconstitution is not to be considered a manufacturing step, and is therefore outside of GMP. It will be important to ensure that the reconstitution and/or other handling is carried out according to the specifications outlined in the CTA or MAA and that no substantial manipulation is performed at that stage. Reconstitution should be viewed as any manipulation that occurs to the finished ATMP at the site (e.g., hospital, treatment center, doctor's office, patient's home, etc.) of administration. The term "reconstitution" could be changed into "handling, preparation and use", see comments above (question 22).
1061 – Question 24	The term "reconstitution" could be changed into "handling, preparation and use" and include any activity after the arrival at the hospital / pharmacy, including the storage, delivery to the point of use, the actual reconstitution as well as the procedure of use / application of the ATMP. 'Reconstitution' could include thawing/warming steps, gentle agitation of the container to distribute cells evenly, change to a different container for administration (e.g. syringe), dilution or suspension in a liquid such as adding a cell concentrate to an infusion bag containing an infusion solution, mixing or compounding at the clinical site. It might also include split of product in several applications and reconstitution and use on several days. Any and all of these options should be fully supported by development activities at the Manufacturer and be described in the Label. An exception could be the dispersion onto a matrix where we would expect that this process would be performed by the

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	manufacturer prior to DP release (e.g. ATMP matrix-applied seeded cultured autologous cells).
1062 – Question 25	Automated devices/systems should be considered as medical devices. GMP may not apply but the hospital or user should have a quality system (such as ISO 9001certification) and ensure proper maintenance, calibration, and cleaning, etc. for automated devices and systems employed. There is a difference between the technical functionality and capability of the automated equipment and the process and product it is used for. The former should be covered by the manufacturer of the equipment and validated by the ATMP manufacturer for its intended use, the latter by the site of use. There should however be agreed upon SOPs between the site and manufacturer for proper maintenance and use for collection/procurement and reconstitution processes. The manufacturer should also employ a site audit schedule and document visits. As stated in the ATMP regulation, any device that is used **in the surgery room**, within one surgery procedure, will not be considered an ATMP, and will not require compliance with the GMPs. The device must be CE marked, with a claim on the performance of the device itself (example, selection of a specific cell sub population, or automated thawing devices). The performance of the device will remain the responsibility of the supplier; the manufacturer of the ATMP will have to validate the use of the device on his specific product and demonstrate lack of impact on quality. The user remains responsible for the final product delivered.