Comments on European Commission Consultation Document
'Good Manufacturing Practice for Advanced Therapy Medicinal Products'
Issued 23-Jul-2015
Ref. http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm

General comments
1. We welcome this consultation and the Commission's desire to ensure that GMP requirements for ATMPs are proportionate and based on risk assessment.
2. We have found it challenging to comment on this document due to differing member company interpretations of its positioning with existing GMP requirements. The absence of cross-references and the extensive copy/paste and paraphrase of existing EudraLex Volume 4 text suggests that the intent is to provide a standalone document which is a 'one stop shop' on GMP for ATMPs. Such a document could be useful, especially for those ATMP producers who are not engaged in mainstream pharmaceutical production. However, as currently drafted, there are significant gaps which would need to be addressed if this document is to stand alone and not create undue risks to patients. For example, there are no definitions of terms or clarification of the starting point of GMP (cf. Eudralex Volume 4, Annex 2, table 1); there are references to "validated" without any details on what is required to achieve validation. There are also concerns that separating this document from the established EudraLex Volume 4 requirements will lead to divergence over time, or an additional burden of maintenance, which would not be of benefit to regulators, manufacturers or patients. The concern about divergence and a reduction in the need for additional detail could be addressed by creating a new Annex to EudraLex Volume 4 specifically covering ATMPs, but extensive editing would be required to turn the current draft into such a document and clarify further those elements which are not applicable to ATMPs or where greater flexibility may be warranted. Whether a standalone document or an Annex, further cross references, e.g. to ICH Q5, as well as EudraLex Volume 4 documents, may be beneficial. **Given the magnitude of the concerns about the positioning of this document and the challenges faced in developing a text for either a standalone or an Annex, we would very much welcome a Commission -Stakeholder meeting (also including the EMA GMP IWG) to discuss this further. Then, following this meeting, we would propose that there is a second consultation draft before the document is finalised.**
3. Some inconsistencies have been identified between the current text and the draft Delegated Act on GMP for IMPs which will need to be resolved. For example, the statement that a register of certifications is not required for investigational ATMPs (Lines 836-838) and the text around packaging and labelling operations not requiring QP certification in Lines 841-846. Where elements are addressed by legislation, e.g., periods for the retention of documents (Lines 427-431), we suggest that direct reference is made to the legislation rather than repeating wording.
4. There is not currently any guidance on GMP for combination ATMPs and it would be beneficial to cover GMP aspects of devices, scaffolds

	and matrices. There should be a clear tie with EU medical device regulations where appropriate and alignment with the US FDA's guidance for industry on GMP for combination products would be beneficial.
5.	The section on starting and raw materials is useful as this is often a challenging area for ATMP manufacturers. Additional points that could usefully be covered here include reference to the EudraLex Volume 4, Part III guidance on 'appropriate GMP' for excipients (2015/C 95/02) ~~could be a useful~~, or at least text drawn from this about assessing the supply chain in accordance with the principles of quality risk management.
6.	There is no coverage within the document currently relating to the shipment of ATMPs and assurance of their quality throughout the supply chain. Drawing from or referring to text in EudraLex Volume 4, Annex 15 and GDP guidance might be useful in this regard.
7.	Given that Hospital Exemption ATMPs are required to be of equivalent quality standard to those for which authorisation is required, and that the fundamental reason for GMP is to safeguard human patients/subjects, these guidelines should also apply to Hospital Exemption products. This should be clearly indicated in the scope of this document.
8.	The scope of this guideline with regards to named patient/compassionate supplies should also be clarified.
9.	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 both the EMA and National competent authorities. We would like to suggest to the Commission to take steps to ensure that the inspections (PAI and/or routine GMP inspections) for ATMPs will be conducted by personnel with good knowledge and expertise in ATMP manufacturing so that the special considerations in the GMP practice tailored for ATMPs can be carried through in the inspections.

Comments on the specific questions raised
Q1: Are the principles laid down in Section 2 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
- Pointing to a risk-based approach is helpful in enabling product and development phase appropriate flexibility whilst ensuring that specific risks are addressed.
Q2: Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline? In the affirmative, please provide examples.
Risk assessment/management is challenging to do well and more information than is given here will be needed to deliver the required outcome. However, it is suggested that this is not the place to provide this additional information. Instead, provide a cross reference to ICH Q9. Separately, over time, consideration might be given to building a set of ATMP-specific case studies to further support organisations in this area.
Q3: How should the quality systems established in accordance with Directive 2004/23[2] be recognised in terms of GMP compliance for products that are ATMPs solely because the use of the relevant cells/tissues is for a different essential function in the recipient as in the donor (i.e. the manufacturing process does not involve any substantial manipulation)? What about the JACIE accreditation system?
- JACIE or equivalent could be recognized as the quality standard for the manufacture of non-substantially manipulated cells/tissues, in particular in early clinical development (non-pivotal trials), since it meets many of the underlying control principles of GMP already. - As these "non-homologous" ATMPs are regulated under directive 2001/83 EC but have the same characteristics as non-substantially manipulated transplant/transfusion products used for the same essential function in the donor and the recipient, which are regulated under Directive 2004/23/EC, as amended, or Directive 2002/98/EC, the technical requirements for donation, procurement, manufacturing, storage and distributions of these products are appropriately covered by JACIE standards. However, the GMP manufacturing license should remain under the responsibilities as laid down in Directive 2001/83 EC. Consequently, we agree that JACIE standards, but not the JACIE accreditation system, could be recognised in terms of GMP compliance for this category of ATMPs.
Q4: Are the requirements laid down in Section 3 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
The fundamental GMP requirements of personnel do not change with stage of development.
Q5: Are the requirements laid down in Section 4 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate..
- Generally the requirements are appropriate with language allowing a risk-based approach in relevant places. See also comments on Question 8
Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?
- Although the 'in general' wording suggests that alternatives are possible, the sentence in Lines 231-233 requiring Grade A with Grade B background is restrictive and does not take account of current accepted practice where isolators are used (Grade C background is commonly used and Grade D background may be acceptable per EudraLex Volume 4, Annex 1, 23), nor does it allow for future technological advances – see comments on Question 8.

- It should not be assumed that higher standards must apply to commercial products. Particularly for autologous cell/gene therapies where there is no change in the scale of production with phase of development, premises for the manufacture of commercial products may well be the same as those used for investigational products. - It should be possible to obtain additional flexibility subject to an appropriate risk-based approach.
Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials
Appropriate premises are fundamental to safeguarding patients/clinical trial subjects and whilst the scale may differ many requirements are independent of phase of clinical trial. Allowance of risk-based approaches adapted to the specifics of the product and manufacturing process, as currently within these guidelines, should enable appropriate action to be taken.
Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)
- Of fundamental importance is the safeguarding of patients/clinical trial subjects. This applies to all phases of clinical trial and to commercial products. The focus should therefore be on performing a detailed evaluation of risk and mitigation of that risk as appropriate to provide the required sterility assurance, not stipulating specific air classification requirements. It is currently recognised that isolators may operate with background air classification less than Grade B. With adequate controls and risk mitigations (e.g., closed systems), it is feasible that background C or D might be appropriate not only for early phase clinical trials but for pivotal trials and commercial production too. A risk-based approach will also leave open the use of future isolator and closed system technology developments which may allow for further relaxation of background air classification, even to unclassified areas in hospitals, irrespective of phase of clinical trial or commercial production. - If further guidance is to be added regarding establishment of the appropriate manufacturing environment for FIM clinical supplies, it would be useful to draw from and align with the text in the FDA guidance document linked below, in particular: • A comprehensive and systematic evaluation of the manufacturing setting (i.e., product environment, equipment, process, personnel, materials) to identify potential hazards • Appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards to safeguard the quality of the FIM investigational ATMP. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf It is not clear why the question includes “with the exception of gene therapy investigational medicinal products”, since we do not see any reason why the above should not apply to ex vivo gene therapy products too.
Q9: Are the requirements laid down in Section 5 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- See specific comments
Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the

text below as appropriate.
- See specific comments
Q11: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?
- The requirements appear to be appropriate. - Traceability will remain an important concern for ATMP products thus documentation should underscore this.
Q12: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.
- All these requirements are equally applicable to investigational ATMPs as part of a robust quality system, based on good documentation practise. - The wording relating to retention of documents for investigational products based on the date of completion or formal discontinuation of a clinical trial is difficult to manage in practice. The manufacturer will want to comply with good documentation practice and archive records as soon as practicable after manufacture and to assign the retention period at this time. Therefore, retention periods are best based on the date of manufacture or date of certification. It is accepted that a longer retention period, e.g., 15 years, may need to be applied if the starting date is earlier.
Q13: Are the requirements laid down in Section 7 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- Generally these requirements are appropriate; some specific comments made. - Additional text flagging the importance of assessing and addressing any adventitious agents (viral or non-viral) for starting and raw materials of biological origin might be helpful. Some other materials, such as magnetic beads, may be critical to ATMP manufacturing processes and should also be risk-assessed and appropriately controlled in the same way.
Q14: Are the requirements laid down in Section 8 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
- Yes, though it might be useful to clarify documentation requirements for seed lot and cell banking systems either here or by reference to relevant parts of Section 6.
Q15: Are the requirements laid down in Section 9 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
- Generally the requirements are appropriate. - Line 648 requires cleaning validation. It is suggested that verification might be acceptable rather than validation, especially for early stages of development. - It is suggested to include a separate section on storage as ATMPs are often products which need specific storage conditions and equipment (e.g., vapour phase of liquid nitrogen).
Q16: Are the general principles laid down in Section 10 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

- We suggest that rather than the wording that "the manufacturing process for investigational ATMPs is not expected to be validated to the extent necessary for commercial ATMPs", which implies the manufacturing processes are expected to be validated to some extent, it is stated that "Manufacturing processes for investigational ATMPs are not required to be validated, but shall be appropriately monitored and controlled, taking into account the stage of product development, in order to assure the quality required for the intended use."
- If this is to be a standalone document, then additional text drawn from EudraLex Volume 4, Part I, Annex 15 should be included here to cover all aspects of qualification and validation (premises, equipment, packaging, transportation, etc., as well as processing). Otherwise, this should be cross-referenced.
- The applicability of this section to critical raw materials is not clear.
- For the validation of cell banks text drawn from EudraLex Volume 4, Part II and reference to ICH Q5 might be useful.
- As per response to Q17, more detail regarding a pragmatic approach to process validation should be developed and included.

Q17: Due to the biological variability inherent in ATMPs and limited batch sizes, process validation is particularly challenging for ATMPs. A pragmatic approach as to the specific requirements on validation should be developed. Please provide suggestions.

- We agree that process validation is particularly challenging for ATMPs and that a pragmatic approach should be developed. We recommend following the 3 stages of process validation prescribed in recent process validation guidance documents, with validation data coming from all 3 Stages rather than just emphasizing Stage 2 with a 3-batch rule. Allow for validation with representative cell type (e.g., from less sick patients, healthy donors, cell line). Emphasize on-going data collection in the continued process validation stage and appropriate adjustments to control strategy based on the knowledge gained throughout product life cycle.
- The principles of process validation can be applied using a risk based approach. Validating the process includes validation throughout the supply chain (raw materials, starting materials, intermediates, drug substances, and the drug product itself, including methodologies). ATMP's pose several challenges, which will require control strategies based on a risk assessment approach (more comments on this to be developed over the coming weeks).
- Also for consideration, there might be the possibility of 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 (IPC/PM) (analogous to PAT) or the release process, and serve 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.

Q18: Are the requirements laid down in Section 11 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

- There are a number of issues with the wording of this section. In particular: Wording in 841-846 is confusing and appears to be in contradiction to Regulation 536/2014. The two-stage release process in Lines 856-873 could also be significantly clarified. It needs to be clear that there is no need for competent authority approval prior to batch release in the event of an unplanned deviation if the points in Lines 875-882 are met.

Q19: Are the requirements laid down in Section 12 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

- There should be no need for samples of starting materials for investigational ATMPs to be kept for a longer period of time based on the completion/discontinuation of the trial. The two years after the release of the product required for commercial products should be long enough.
- Flexibility is required with regards to reference and retention samples for autologous products where the intent if for the entire manufactured

batch to be dosed back to the patient. It should be possible to minimise the size of reference samples, e.g., by keeping samples from the latter stages of production rather than the finished product or by reliance on in-process testing to justify 'if tested, would comply' for certain tests and therefore not need to keep sufficient samples to repeat these analytical tests. With regards to retention samples, a fully packaged unit cannot be kept as this would be the only unit. Inclusion of text that allows use of label copy in batch records or other means, such as photographs, in place of a retention sample would be very beneficial.

- Section 12.4 on stability monitoring program does not include any text around setting of expiry dates and it would be useful to include reference here to ICH Q5C. Specifics relating to stability testing, including container-closure integrity testing, for cryopreserved products might be helpful too.

Q20: Are the requirements laid down in Section 13 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

- The text is generally appropriate, but the scope should be any 'GMP activities' that are outsourced, not just 'manufacturing activities', and the proposed text confuses contracting and subcontracting – see specific comments.

Q21: Are the requirements laid down in Section 14 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.

- Given the recent revision of EudraLex Volume 4, Chapter 8, to provide greater detail in response to issues identified by competent authorities, it is surprising that this section is so light. It seems to assume that 'complaint' and 'quality defect' are synonymous, which they are not – not all complaints relate to quality defects and not all quality defects are identified via complaints. There is no mention of the involvement of the qualified person, nor is there any tie with processes for dealing with suspected adverse (clinical) events.

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

Q22: Do you agree with the principle that, where reconstitution of the finished ATMP is required, the manufacturer's responsibility is limited to the validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users?

- Yes, we agree with this principle.
- The responsibility of the manufacture should be limited to the development of the processes to be implemented at the ~~infusion~~ administration site, be it e.g., thawing and resuspension, reconstitution, or dilution.
- Detailed instructions should be provided to the users. These should highlight any particular facility/equipment or training requirements to ensure safe and accurate processing together with information on storage.
  Where dilution is to be carried out, the manufacturer should specify the "diluent" to be used, or provide it if required.

Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?

- Yes, we agree that reconstitution is not manufacturing and is therefore outside GMP; this should fall under the remit of general hospital medication preparation by pharmacy, nursing or other appropriate health care professionals.
- Appropriate measures should be taken to prevent (cross) contamination during reconstitution. These activities fall outside the scope of GMP and should be part of the pharmacy manual or Physician's instruction.

Q24: What activities should, in your view, be considered as reconstitution?
- Reconstitution could include: Thawing steps, dilution, gentle agitation of the container to distribute cells evenly, preparation for administration, e.g., drawing up of a cell suspension into a syringe, or adding a cell concentrate to an infusion bag containing an infusion solution and attaching an administration set. - It might also include splitting the product into several aliquots for reconstitution and use in separate doses over a period of time supported by development activities and described in label/supporting documentation..
Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges. *Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?*
- We would like to work towards a vision for autologous therapies which would enable fully automated cell processing at a patient's bedside with cells being taken, loaded into the equipment and sometime later the finished product being taken for administration. Currently, in addition to the technological barriers that remain to be overcome to enable such processing to be performed in an unclassified area, we believe there is a legal impediment to this: Because such processing is likely to be interpreted as manufacture, it therefore needs to take place in a licensed facility with QP certification. Therefore, in parallel with work to address the technical challenges and flexibility to enable processing to be performed in an unclassified area such as a hospital, we would like to see work progressed that would remove this impediment. Defining responsibilities would be challenging and should be subject to written contract. - The GMP obligations need to be covered by the site of use of the automated equipment. The manufacturer should be obliged to support with all necessary information the responsibilities of the site of use. 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, the latter by ATMP manufacturer and the site of use. - The applicable devices may not fall under the GMP system, but follow good quality systems under the medical device legislation.

Specific text comments				
# section	**Line no.**	**Comment / Rationale**	**Proposed change / suggested text**	**Classification of importance** **H**= high **M**= medium **L**= low
HIGH				
1	73/74	Why exempt the manufacture of ATMPs under Hospital Exemption from the scope of GMP? Whenever a product is produced for human administration GMP should be applicable.	Remove the exclusion of Hospital Exemption manufacture from the scope.	H
4.2.2	214/215	Facilities and equipment are 'qualified' rather than 'validated' Further, the term "fully validated" is used, but the meaning of this is not given. It is suggested that cross-reference is included to Volume 4, Part 1, Annex 15.	"For commercial production of ATMPs, the premises should be fully **qualified in accordance with [EudraLex Volume 4, Part 1, Annex 15, or cross reference to additional detail within this document]**."	H
4.2.2	214/215	No guidance is provided on qualification of premises for P1/2 and P3 investigational ATMP manufacture.	Proposed addition: "**For investigational ATMPs, the HVAC system / laminar air flow hoods should be qualified and premises should be monitored**"	H
4.2.2	230-233	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. This is independent of the clinical stage of development.		H
4.2.2	231	The proposed wording is not consistent with current manufacturing for injectables when carried out within an isolator (Grade C background frequently used and EudraLex Volume 4, Annex 1, 23, allows for the possibility of isolators to be operated in a Grade D environment).	That statement should be qualified to state unless carried out in a closed system…	H
4.2.2	232	Please see comment to line 231 above. With adequate controls and risk mitigations (e.g., use of	Change "In general, an A grade with a background of B grade is required for pivotal clinical trials and	H

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		closed systems) this should be acceptable not just for early phase trials but also for commercial manufacturing. Future ATMPs will need some innovative manufacturing solutions which may not fit current sterile manufacturing paradigms. The requirements should therefore be flexible with a focus on detailed evaluation of risk and mitigation of that risk to provide the required sterility assurance.	commercial production" to: "Air classifications should be determined and justified through risk assessment to assure product sterility taking into account the nature of the product and its processing, including consideration of operational enclosure."	
5	294-296	Given all the current concerns about data integrity, this section is far too light. Reference to, or text from, Volume 4, Part 1, Annex 11, should be included here. In particular, there should be text included regarding the importance of data audit trails.		H
6.5	428-431	Good documentation practice will archive records as soon as practical after their creation and assign the retention period at the time of archive. Therefore, it is preferable to set the retention period based on a date that is already known, e.g., date of manufacture, rather than on a future date, such as 'completion or formal discontinuation of the last clinical trial in which the batch is used'.	Suggest: "For investigational medicinal products, the batch documentation must be kept for at least 15 years after the date of manufacture."	H
8	541-543	In the sentence "Cell stock changes should be addressed in the marketing authorisation and the conditions therein should be complied with", is the term "cell stock changes" should include introduction of new cell bank(s) obtained from new donors.	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.	H
9.3	644/645	'concurrent manufacture in the same area' It need to be clarified what is meant by 'area'. For example, if vectors are processed within isolators, is it the isolator that is the 'area', or the room in which the	Clarify. Propose that an isolator could be defined as an 'area'.	H

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		isolator is situated? If the former, then more than one isolator could be in a room and it would be possible to process vectors at the same time, subject to appropriate assessment and mitigation of any associated risks. If the latter, then only one isolator could be used at any given time.		
11.3.1 (ii)	841-846	This paragraph is confusing with regards to definition of manufacture/manufacturing authorisations. If packaging and labelling is carried out at a sponsor site, then it should clearly be an authorised site and require a QP certification. There is no exemption for sponsor sites in Reg 536/2014, Article 61(5)(a). Any exemption for hospitals, health centres and clinics needs clearer definition.		H
12.2	924	The requirement to retain a fully packaged unit of the finished product cannot be achieved for some autologous products, where the entire batch may be a single unit.	Alternative ways of meeting the need for identification, e.g., label copy in batch records, photographs, should be allowable.	H
MEDIUM				
2	94-95	Self-inspections are expected, but there are no further details provided. See also comment to lines 1056-1057	Add in a section on self-inspections based on EudraLex Volume 4, Chapter 9	M
2.1	104	The RBA is supposed to also include an assessment of the potential safety and (for pivotal investigational ATMPs and commercial ATMPs) efficacy implications.	Add extra line: The RBA is supposed to take quality (and consistency) of the product into account but should also include an assessment of the potential safety and (for pivotal investigational ATMPs and commercial ATMPs) efficacy implications.	M
2.1	113/114	As mentioned before (line 104), the RBA is supposed to assess quality, safety and efficacy (e.g., patient population, disease, route of administration) impacts. This should be clearly highlighted.	…with the need to ensure the quality, **safety and efficacy** of the product.	M

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3	130-134	It is suggested to provide more details on the specific training requirements for staff and key personnel handling ATMPs (e.g., due to the potential contamination of biological starting and raw materials with adventitious agents, short shelf-life of intermediates and final product, the fragile nature of tissues and cells, the complexity of a combination product, and additional manufacturing steps in the clinic). Additional guidance on the handling of GMOs is suggested. This could also be covered in Section 16 on environmental monitoring of GTs.		M
3	138/139	The appropriate protective equipment for operations is open to interpretation. Additional guidance would be useful. It does not connect gowning requirements also to the environmental controls necessary for the protection of the product. There is no connection to training and qualification of operators gowning appropriately.		M
3	140-143	This should be a two-way protection as there is not only the potential contamination of the product with adventitious and other agents coming from the operator but also the risk for communicable diseases transferred from biological starting and raw materials to the operators. Also personal handling GMOs may require additional training to prevent from cross-contamination risks and potential environmental impacts.	Add two sentences in line 142. **In addition, personal should be trained and appropriate personal protection should be in place to prevent transfer of communicable diseases from biological raw and starting materials to the operators. Personal handling GMOs may require additional training to prevent from cross-contamination risks and potential environmental impacts.**	M
3	144-147	This section states, “Health monitoring of staff should be proportional to the risks. Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated.” While we appreciate the qualifying phrase “proportional to		M

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		risk" again recognizing the application of flexible standards, the statement is quite broad. Additional guidance on vaccination would be useful. Should all personnel receive Hepatitis B vaccine?		
4.2.1	185-188	Biosafety, including GMO aspects, should apply and be mentioned at the very beginning of the guideline.		M
4.2.1	188-189	A RBA should be taken to assess the possibility to use a multi-product facility. This would include, but is not limited to autologous versus allogeneic nature of the ATMP treatment, use of genetically modified organisms in the facility, the use of antibiotics in the manufacturing process and the source and origin of raw and starting materials.	Add a sentence after line 189. **A RBA should be taken to assess the possibility to use a multi-product facility. This would include, but is not limited to autologous versus allogeneic nature of the ATMP treatment, use of genetically modified organisms in the facility, the use of antibiotics in the manufacturing process and the source and origin of raw and starting materials.**	M
4.2.2	216-219	The degree of environment control and monitoring is not clearly described.	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, airflow direction, temperature, relative humidity, viable and non-viable particulates, critical surfaces, equipment, and personnel (when appropriate). Annual review of environmental data and trend analysis should be performed by manufacturers to verify the maintenance of effective environmental controls.	M
5	280-282	Cleaning needs to be carried out in accordance with a written procedure and there should also be controls over cleaned equipment. It needs to be ensured that cleaning equipment is not a source of contamination.	Add extra text drawing from Volume 4, Part 1, 3.36/3.37. E.g., "The equipment must be cleaned **and stored** appropriately **in accordance with written procedure** in order not to be a source of contamination. **Washing**	M

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			and cleaning equipment should be chosen and used in ways that ensure they do not become a source of contamination. Single-use, disposable, **equipment parts** should be used where posible. Sterilisation of multi-use…"	
5	288-293	Lines 291-293 essentially repeats lines 288-290.	Delete lines 291-293	M
6	299-441	There is nothing here about documents being appropriately authorised and dated.		M
6	299-441	There is reference to SOPs in Line 306 and to procedures being applied to qualification/validation and investigations in Section 6.4. There are, however, no stated requirements for procedures to be used to ensure this documentation is delivered.		M
6.3	320	It is suggested to define excipients little further and include excipients. See also GMP for excipients (2015/C 95/02) and EudraLex Volume 4, Part III guidance on 'appropriate GMP' for excipients	The specifications of **raw and starting** materials, **other materials coming into contact with the active substances and excipients** to be used…	M
6.3	322/323	As the experience of many of the manufacturers of early development studies is varied, it is advised to provide some additional guidance around expectations of a "consistent" manufacture for FIM/phase 2 and pivotal trials, e.g., when should IPCs and PMTs be defined, at what stage of development should acceptance criteria be numerical values, how to approach consistency in case of an (ultra-) orphan indication, where few batches are manufactured during product development.		M
6.3	341	Suggest that storage conditions should also be specified.	Suggest: "**Storage conditions and** maximum period of storage"	M

Specific text comments				
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6.3	343/344	It is advised to consider back-up suppliers of critical raw materials already at the pivotal clinical development stage, as changes to third party suppliers, hence raw materials, could potentially have huge impact on the product quality, safety and/or efficacy.	Add sentence to line 344: **Back-up suppliers should be considered for critical raw materials during late clinical development.**	M
6.3	345-353	As starting materials of ATMPs are often of biological origin, it is advised to include here or in section 7 on "Starting and raw materials" some wording around "donor eligibility" and meeting the requirements as laid down in directive 2004/23/EC, as amended, directive 2002/98/EC and guideline on xenogeneic CBMPs.		M
6.3	346-353	There is no mention of any sampling within this set of requirements	Add in: "Instructions for sampling and testing, as appropriate."	M
6.3	368-372	In many cases, the "packaging" of a cell/tissue based product is for a single patient. This section should be modified to address traceability (see also general comment on tracking and traceability) through the entire supply chain which goes beyond "reconciliation" of a small number of packaged units, which may be applicable to off-the shelf allogeneic products and off-the shelf gene therapy products.		M
6.5	426-441	This is an example of inconsistency with current and draft guidances. This is not consistent with the Delegated act on GMP for IMP. Comments in this area will be made in the response to the consultation on the CTR delegated act on GMP for IMP.		M
6.5	432-437	Concern about the practicality of these requirements. Suggest that a maximum period of time is allowed for, e.g., 30 years, after which documentation does not need		M

Specific text comments				
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		to be kept?		
6.5	438-441	A 30 year (after the expiry data of the product) record retention requirement for any material coming into contact with cells/tissues may prove to be quite burdensome to sponsors. We encourage some flexibility in the amount of documentation kept per batch. For example, retaining only final product records (as long as all materials can be traced back to their source) rather than retaining all incoming and processing records for the entire retention period.		M
7	450	Reference to the EudraLex Volume 4, Part III guidance on 'appropriate GMP' for excipients could be a useful reference to add in here, or at least a statement about assessing the supply chain in accordance with the principles of quality risk management.		M
7	485-488	Prior to stating that where possible, sterilization of starting materials and raw materials should be performed by heat, 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 in other parts of the document, the guidance should be based on applying knowledge of the material and appropriate evaluation for risk. All of the techniques can be considered as effective when appropriately applied and verified, and therefore, one should not be emphasized over another. Where possible the choice of sterilization method follows the decision tree. http://www.ema.europa.eu/docs/en_GB/document_librar		M

Specific text comments				
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		y/Scientific_guideline/2009/09/WC500003520.pdf		
7	487-488	Comment: it is suggested to include some wording around the need for proper validation of these inactivation steps, ideally prior to FIM, but latest prior to commencing pivotal clinical trials.	Add sentence after line 488: **The inactivation method of biological materials should be validated, latest prior to starting pivotal clinical trials.**	M
7	490-492	To assure no antibiotic process impurities are present in the final product, the adequate removal of the antibiotic should be part of process validation. This process impurity should be tested for at a relevant stage in the manufacturing process, at the latest prior to commencing pivotal clinical trials. It is discouraged to use β-lactam antibiotics in the manufacturing process and if used, to replace by other antibiotics. In case of a detectable amount of antibiotic present in the final product, this should be clearly stated on the product label.	Add two sentences: **This process impurity should be tested for at a relevant stage in the manufacturing process, at the latest prior to commencing pivotal clinical trials. The adequate removal of the antibiotic should be part of process validation.**	M
8	555-557	In the cases of lack of GMP compliance of cell stocks/cell banks and viral seed stocks, a risk assessment should be performed to assess for the potential impact on product Q/S/E. Additional testing of the starting material, stocks/banks, intermediates and/or finished product may be required.	Change sentence to: "In these cases, the lack of GMP compliance may require additional testing **of the starting material, stocks/banks, intermediates and/or finished product, based on a risk assessment for impact on product Q/S/E."**	M
9.1	561	Often ATMPs are stored frozen and labelling should take place directly after filling of the primary container and after packaging into the secondary packaging material. It is suggested to include a section on labelling (see also general comment with some suggestions as to what needs to be addressed).		M
9.1	562 and	It is suggested to provide some guidance on what is meant by "consistent manufacture", taking the stage of		M

Specific text comments				
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	570	development into account as well as the inherent variability of biological starting materials, especially for autologous products. See comment lines 322-323.		
9.1	577-579	This sentence is pretty vague. It is advised to provide some additional verbiage on criticality analysis and defining in-process controls and process monitoring tests and what is expected at which stage of development. Generally, it is recommended to monitor all presumptive critical process parameters ((P)CPPs) in early development and define IPCs with acceptance criteria and PMTs based on criticality analysis prior to starting pivotal trials or latest prior to MAA. Especially for autologous and allogeneic 1:1 products, plenty of data are becoming available during the cause of product development. Unfortunately, this is a challenge or impossible for (ultra-) orphan (off- the shelf) products.		M
9.3	649	At the beginning of the development process a completed cleaning validation is hard, if not impossible to achieve, cleaning verification based on risk analysis should be acceptable.	Add the following sentence at the end of line 649: **"For first in human studies, a cleaning verification based on risk analysis is acceptable."**	M
9.5	677-685	Functional secondary packaging materials (e.g., to protect from light, humidity, to prevent from temperature excursions) may also be addressed here, as are also of importance.	Proposed change to line 778: "The suitability of primary **and functional secondary packaging materials**…"	M
9.6	687-689	As acknowledged in other parts of this document, many cell/tissue based products 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, that is not clear in the way this document is currently		M

Specific text comments				
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		written.		
9.7	698-701	It is not clear what is meant by "authorized procedure". Re-processing of rejected products must follow a procedure approved by the competent authorities under a CTA or MAA or otherwise authorized by manufacturer's QA&QP.	"…..with a defined a procedure **approved by the competent authorities under a CTA or MAA or otherwise authorized by manufacturer's QA&QP,** after evaluation of the risks involved.	M
10	708-727	Consider incorporation of additional text to suggest an approach to validation. It is suggested to take a reduced validation approach compared to Eudralex Volume 4, Annex 1, particularly for (ultra)-orphan off-the shelf products, where the operating personnel spend more time doing process simulation than actual manufacturing. I.e., it is a huge constraint for a manual process with many manufacturing steps, hence process simulations could be considered for process validation purposes.	A pragmatic approach to validation is proposed where traditional process performance qualification is not possible (e.g. autologous therapies for which use of patient material would not be feasible or ethical). Extensive process development data using well understood model systems and data from production of clinical trial material in conjunction with continued process verification during commercial production could be considered equivalent to traditional process validation used for conventional pharmaceuticals. The data obtained from the model systems would be complemented with knowledge obtained from the development program and targeted smaller scale studies using representative starting material. Together these studies could adequately demonstrate that the quality attributes of the process are robustly controlled. To further demonstrate that the process control strategy is adequate to generate product with the defined critical quality attributes despite the variability associated with starting material from the patient, a continued process verification approach is proposed. Additional sampling for characterization	M

Specific text comments				
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			testing may be incorporated into the production process, as possible without compromising patient safety and efficacy. The number of validation batches should be determined by the manufacturer on a case-by-case basis and a risk-based approach should be taken. Aspects to be taking into account are: variability of the starting material (i.e., autologous and allogeneic 1 donor: 1 recipient cell/tissue products may require a higher number of validation batches than non-cellular gene therapy products), the clinical application (e.g., for ultra-orphan indications, only a few batches may be manufactured during the products' clinical development programme, hence full-process validation may be a post-approval commitment), complexity of the manufacturing process (e.g., number cell/tissue manipulations), etcetera. In case less than 3 batches are used for process validation, this needs an extensive justification (RBA).	
10	723/724	Significant changes during clinical product development and after commercialization require a comparability study. Significant changes should only be validated once the pre-change process is validated, hence prior to MAA and post-market.	"**Significant changes may affect the reproducibility of the process and quality/consistency, safety and/or efficacy of the product and should be assessed through a comparability study. Significant changes of a validated process require a re-validation**."	M
11.2	742-791	It is advised to provide some guidance on how the QP responsibilities tie into the responsibilities of the Responsible Person at the procurement site of human/animal derived starting materials.		M
11.2	749-	For FIM investigational ATMPs, manufactured in 3rd		M

Specific text comments				
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	752	countries, e.g., the USA, a less stringent GMP regiment (e.g., class A in class C background) may be acceptable, in case appropriate in-process, release and patient safety measures are in place. See comments for Q8.		
11.2	749-752	The wording in this section should be in alignment with the final wording of the CTR Delegated acts.		M
11.2	768/769	It is suggested to provide some additional guidance on the kind of knowledge and experiences QPs releasing ATMPs should have E.g., scientific background, on the job training or additional courses in the field of the specifics of gene therapies, tissues and cells, cell processing and characterisation, potency testing, flow cytometry and other test methods unique to these products. For combined ATMPs, the QP should have a good understanding of the device/scaffold specifics.		M
11.2	773/774	According to Annex 13 of the EudraLex volume 4, a product specification file (PSF) must be in place for investigational ATMPs and may be assessed by the QP as part of the release process. It is suggested to include some additional wording from these guidances re. QP duties and include in this document.		M
11.3.1 (ii)	836-838	Wording not consistent with the CTR Delegated acts – risk of divergence and no benefit is perceived in the text being different to the Delegated acts.		M
11.3.1 (ii)	838-840	A retention period based on the completion or formal discontinuation of the last clinical trial in which the batch is used is difficult to manage. Good documentation practice is for documents to be archived as quickly as possible and for the retention period to be set at time of archive. A fixed period, as for commercial	"For investigational ATMPs, the register or equivalent certification documentation must be kept for at least ten years after certification of the batch by the QP."	M

Specific text comments				
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		ATMPs, would be better. To allow for the additional time associated with trial completion, a period of ten years from date of certification is suggested.		
11.3.1 (ii)	841	Wording not consistent with the CTR delegated acts.		M
11.3.1 /11.3. 2	856-873	This section appears to relate to the two-stage release process that may be applicable to short shelf life products which require administration before it is possible to complete full analytical testing and full release of the product, but would benefit from greater clarity.	"**Where specified in the marketing authorisation or clinical trial authorisation, ATMPs with short shelf lives requiring administration before it is possible to complete all quality control tests, may be subject to a two-stage certification and release process:** - Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures, and the available analytical results for review in preparation for the initial certification by the QP**, which allows release for administration**. - Assessment of the final analytical tests and other information available for final certification by the QP. **A procedure should be in place detailing the whole release process, including** responsibilities of the involved personnel and the continuous assessment of **batch data between the initial and final certification. The procedure should include description of** the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained after the **initial QP certification and release for administration (under restriction), thus preventing final certification.** Such events should be fully investigated..."	M

Specific text comments				
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11.3.1 /11.3. 2	856-873	Should include minimum tests to be completed for stage 1 release	Add in: "Minimum testing required for Stage 1 release/certification must be defined in site processes/procedures".	M
11.4	875	Delete 'active substances' and 'excipients' from this text as these are not subject to QP certification.	"As long as the product specifications are met..."	M
11.4	883-885	This should be reworded to make it clear that the requirement is a notification only and that no response is required from the competent authority before product release. It is also suggested that this is equally applicable to commercial ATMPs. 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. It is suggested to replace the word "significant" to "unplanned"	"Information on batches certified following such an unplanned deviation should be notified to the relevant competent authority"	M
12.2	931/932	Scarcity or nature (e.g., stability) of starting material of biological origin may not allow for spare samples. This does not only apply to starting materials of biological origin, but sometimes also to active substances, intermediate, bulk and finished products of biological origin.	"For biological starting materials, **active substances, intermediate, bulk and finished products,** sampling is often not justified…"	M
12.2	940-942	There is no justification for samples of starting materials for IMP ATMPs being kept for a longer period of time based on the completion/discontinuation of the trial. The two years after the release of the product required of lines 938/939 should be long enough in all cases.	Delete the sentence "For investigational ATMPs..."	M
12.2	943	It is not clear whether the shorter periods that 'may be acceptable' are down to manufacturer justification or whether these need to be included in CTA/MAA or	Suggest change to "...therefore, shorter periods may be applied when supported by a written justification by the manufacturer."	M

Specific text comments				
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		otherwise agreed with regulators.		
12.2	946-949	Whilst the flexibility is of some benefit, from a guidance perspective some additional text here around the considerations of sample storage under label storage conditions or conditions that maximise stability might be beneficial. This is especially the case for short shelf life products.	Suggest: "Reference samples should usually be kept at the label storage conditions so that they are fully representative of the product that has been supplied. For products with short shelf life, however, samples at label storage conditions will rapidly cease to serve any useful purpose and in such circumstances the use of alternative storage conditions that maximise stability should be carefully considered and the decision documented."	M
12.3	957/958	For tissue and cell based ATMPs, it may not always be feasible to establish active substance/finished product reference materials and standards. The approach taken by the manufacturer should be justified in the CTA/MAA.		M
12.3	974/975	Some additional guidance may be needed to explain that in certain circumstances, intermediate testing or in-process control results may be used to release the final material (intended material), if justified and approved by the competent authorities in the CTA/MAA.	Testing of intermediates **instead of the intended material** or **in-process testing instead of final release testing is acceptable**, if the relevance of the results from these tests to the intended material can be demonstrated. **The approach taken should be defined in the CTA/MAA**.	M
12.4	1000-1007	It is suggested to provide some guidance on stability studies during clinical development, type of studies (real time studies, stress studies, in-use stability studies), type of materials to be put on stability (intermediate, active substance, finished product, combined ATMP, critical raw material dispensed and stored at the manufacturing site), the challenges around stability studies on autologous cell and tissue based products, etc. This topic		M

Specific text comments				
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		could also be covered in a separate document.		
12.4	1000-1007	In cases of short shelf life or limited availability of the material, the feedback for biological characteristics from the clinical team for each single ATMP should be careful analysed and trended.		M
13	1008-1034	Outsourced activities should preclude the organizations showing compliance with Directive 2004/23/EC[2] or Directive 2002/98/EC[4]. This should include the (micro-) biological laboratories at those sites as certain tests on pathogenic organisms will be extremely difficult to outsource elsewhere.		M
13.1	1010	This sets the scope as 'manufacturing activities that are outsourced' but per EudraLex Volume 4, Chapter 7, there may be other GMP activities which do not fall within the definition of 'manufacturing' which are outsourced and these too should be managed according to this section.	Suggest: "~~**Manufacturing**~~ **Any GMP** activities that are outsourced..."	M
14.1	1037/ 1038	Additional text based on Eudralex Volume 4, 8.9 on elements to be covered as part of a quality defect investigation would be useful here.		M
14.2	1053-1056	Additional information on product recall from EudraLex Volume 4, 8.20 – 8.31 could usefully be included here.	E.g., more detail about "how the recalled material should be treated"; tracking the progress of a recall and its close out; testing effectiveness of arrangements.	M
14.2	1054-1056	In cases where the ATMP was already administered, the process for notification of the Health Care Provider and the competent authority should be addressed in both the clinical stage of development as well as for a marketed ATMP. This procedure should be provided in the CTA/MAA.		M

Specific text comments				
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After 14.2	Between 1056 and 1057	Self-inspections are expected per lines 94-96 in Section 2, but there are no further details provided.	Add in a section on self-inspections based on or referring to EudraLex Volume 4, Chapter 9	M
15	1067-1060	It is advised to refer to appropriate EMA GMO guidances or include some wording in this guidance. For investigational ATMPs it is worth notifying the manufacturer of the obligations to meet country specific GMO obligations.		M
LOW				
1	62	It is suggested to include a few more examples for intrinsic variability.	(such as…..not well characterized active substances)	L
2	81	There is no mention of the control of outsourced activities within this listing	Add in that "Any outsourced activities are governed by a written contract which clearly establishes the scope of work, required standards and responsibilities of each party.	L
2	88	not only to assure quality, but also consistency of the product	the production process is adequate to ensure the quality **and consistency** of the product, …	L
2.1	107	One example is not clear enough, more complex manipulations should also be cited	Change text in brackets to: "(e.g. cultivation of cells, **manipulations altering the function of cells**, **like cell differentiation and genetic modification of cells, combination of cells or tissues with devices/scaffolds**)"	L
2.1	107/108	The manufacturing and testing challenges posed to autologous ATMPs do also apply, at least to a certain extent, to allogeneic 1 donor: 1 recipient ATMPs and ATMPs used for the treatment of (ultra) orphan diseases (i.e., lack of number of batches produced to develop appropriate process and product acceptance criteria, the number of batches available for process evaluation,	In addition, the manufacture and testing of autologous ATMPs, **allogeneic 1 donor:1 recipient ATMPs, and ATMPs used for the treatment of (ultra) orphan indications** poses…	L

Specific text comments				
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		process validation, and to show batch-to-batch consistency).		
2.1	115-122	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.	Suggest that the flexibility be tied to product knowledge and re-emphasize that product "safety" from a microbial content or an adventitious agent standpoint should still be ensured. Perhaps also restate that facility cleanliness concepts, personnel training, and equipment calibration would still be required.	L
2.1	115-122	It is suggested to include following wording from Chapter 1 of Eudralex Volume 4: Quality Risk Management Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively. The principles of quality risk management are that: i. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient ii. The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.	It is suggested to include following wording from Chapter 1 of Eudralex Volume 4: Quality Risk Management Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively. The principles of quality risk management are that: i. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient ii. The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.	L
2.1	123-125	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 be lacking. Many of these manufacturers of early trials have limited knowledge regarding requirements to with regard to GMP,	Provide an example of such ' specific risks' upon which 'additional measures'	L

Specific text comments				
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		expecting they have the capability to interpret that statement is an inaccuracy. The manufacturer should not only consider additional quality measures, but also additional clinical safety measures, when applying the RBA to address the specific risks of the product.		
3	132	"understanding of its tasks..."	"understanding of **their** tasks..."	L
3	147-151	Any additional guidance on the concept of cross-contamination is suggested (see also answer to Q4). E.g., examples focused on the differences in potential risks for (cross) contamination of allogeneic cell therapies and autologous This same comment is valid for lines 162-166 in the following section, but with respect to facility design and facility flows.		L
3	152-154	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 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.	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 **and independent** ~~by senior management~~."	L
3	152 – 156	This text could usefully be expanded to make clear the requirement for job descriptions and to ensure that there are no gaps in responsibilities.		L
3	153	Specific qualifications for QPs releasing ATMPs are not addressed in this document. It is suggested to specify the qualifications in more detail and harmonise across Europe and cover in this or another document. See also		L

Specific text comments				
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		sections 11.1 and 11.2.		
4.1	168	Include the requirement for cleaning to be covered by written procedure.	"Premises should be kept clean by cleaning and, where applicable, disinfecting according to detailed written procedures."	L
4.1	179-181	There is no globally consistent definition of cytotoxic agent and is not used in Eudralex Volume 4, Chapter 5. Many oncology products could fall into this category if verbiage left in resulting in facilities that could not be used. This is an unnecessary restriction, would be an undue burden on manufacturers and prevent product from being made in what otherwise would be deemed a suitable facility. Suggest to delete.	Delete "or cytotoxic agents" from line 180.	L
4.2.1	187	Just grammar and use of proper nouns	(i.e., Biosafety Level 3 or 4)	L
4.2.1	202	"The laid out of the premises..."	"The **layout** of the premises..."	L
4.2.1	205-207	The environment classification is not described		L
4.2.1	205-207	There is not a clear description of Air locks and pass through with pressure differential, interlocks and timing when doors can be open.		L
4.2.2	210/211	Suggest delete the sentence "Special attention should be paid to products for which there is no sterilisation of the finished product" because this will be the routine situation for ATMPs and the converse situation is covered by the sentence in Lines 212-214	Delete the sentence "Special attention should be paid to products for which there is no sterilisation of the finished product"	L
4.2.2	212-214	Perhaps the author meant to write the following	"The measures implemented to ensure an aseptic environment should be adequate having regard to all the specific risks of the product. If sterilisation of the finished product is not possible, particular attention should be paid to the filling process."	L

Specific text comments				
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4.2.3	240	"In the case of large scale production" is redundant here, since the wording "drains should be of adequate size" takes account of the scale of production.	Delete "In the case of large scale production" and start "Drains should be of adequate size..."	L
4.2.3	244	Suggest "Developers" should be "Manufacturers"	"Manufacturers are reminded that..."	L
4.2.3	246	"Clean areas ..." The use of 'Classified Grade A/B areas' would avoid risk of confusion from use of word 'clean', since all premises should be kept clean (168) and drains may be appropriate in places.	"Classified Grade A/B areas should not have drains installed."	L
4.3	261	Draft text here has "Highly **re**active" vs "Highly active" of Volume 4, Part 1, 3.24. Perhaps both should be covered?	"Highly active or reactive materials and products should be assessed to ensure their appropriate safe and secure storage."	L
4.4	266/267	Reference is made to further details about quality control laboratories in Section 12.1, but this section does not include further details about testing facilities.	Incorporate here (and remove reference to Section 12.1) or within Section 12.1 (retaining existing wording here) the further details required.	L
5	294	This sentence does not read quite right.	Suggest: "There should be sufficient controls to prevent unauthorised access to data which would enable changes to be made."	L
6	299-441	There is nothing here about documentation of batch release/rejection or of distribution.		L
6.1	301	Typo	"... and is **a** key element of ..."	L
6.1	313	Why should only commercial manufacturing sites require site master files? The creation of a site master file is a useful exercise to ensuring that key quality systems are in place and is therefore of benefit for any facility producing products intended for human use.	Delete 'commercial': "A site master file should be prepared for every site involved in manufacturing."	L
6.3	323/324	Does not read quite right.	Suggest "... **complies with the relevant quality specifications**."	L
6.3	325	Specifications shouldn't not only be assessed and	Specifications and instructions should be periodically	L

Specific text comments				
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		updated based on current technology and regulatory requirements during product development, but also post-approval. This is a life-cycle exercise.	re-assessed **for investigational and commercial ATMPs (or during development and post-approval)** and be updated as necessary.	
6.3	329	Add commercial product, as this is a lifecycle exercise.	change **on investigational or commercial** product quality and any ongoing clinical trial	L
6.3	330	Does not read quite right.	Delete 'It is recalled that' and subsequent minor grammatical changes; separate sentence for IMPs: "**Changes to** the manufacturing requirements approved as part of the marketing authorisation must be agreed by the competent authorities. **Substantial modifications**..."	L
6.3	336-353	It is suggested to either cross refer to the specifications for raw and starting materials in section 7 (lines 442 and further) or to include the specifications for these materials in section 7 and cross-refer in this section to section 7. Same applies to section 9.2 on Handling of incoming materials.		L
6.3	337-339	Suggest appropriate regard of risks for IMPs needs to be documented and that consideration should also be given as to minimum testing, not just relying on manufacturer's certificate of analysis.	Suggest: "For investigational ATMPs, the manufacturer may rely on the certificate of analysis of the supplier **if justified in a documented risk assessment. Consideration should still be given to minimum testing to assure quality.**"	L
6.3	347/348	Often, third party suppliers of ATMP starting materials are tissue establishments, procurement organisations and hospital blood banks. It is suggested to add this.	Contracts and quality agreements with third party suppliers **(e.g., tissue establishments, procurement organisations and hospital blood banks)** should be kept.	L
6.3	354/355	Add line on specifications for excipients	Add sentence after line 355: **For excipients not covered by the Ph. Eur., the pharmacopoeia of an EU member State, USP or JP, an in-house**	L

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			specification should be available and documented.	
6.3	365/366	Non-phamacopoeial excipients and other materials coming into contact with the active substance(s) are missing	Release and rejection criteria for raw and starting materials, **other materials coming into contact with the starting materials and/or active substances, non-pharmacopoeial excipients**, intermediates, bulk and finished product….	L
6.3	366	The wording " release strategy for characterisation results "is confusing, as the release of a substance/intermediate/bulk/ finished product is based on the release specifications (methods + acceptance criteria). Additional (in-process and/or product) characterisation testing may be performed, but the results are not required to be part of the CoA, hence to be available prior to release of the material. Otherwise, it would be part of the release specifications.	Replace "the word "characterisation" by "**test**".	L
6.3	375/376	Additional wording to be provided, for clarification.	Instructions for product preparation prior to administration, if applicable, e.g., thawing procedure, **should be developed in detail and provided by the sponsor for the clinical setting, and is expected to be part of the label for approved medicinal products commercial ATMPs**.	L
6.2.2	377	Should be 6.4, not 6.2.2	Correct and address knock-on impact on Lines 420 and 426, i.e. change to 6.5 and 6.6, respectively.	L
6.2.2	378/379	The sentence contains the following phrase, "any **significant** deviations should be recorded and investigated" Inclusion of "significant" could prove to be problematic since it then leaves it open to judgement what level of deviation constitutes a significant deviation. Would suggest consideration be given to remove "significant" from the sentence. See also	Any ~~significant~~ **unplanned** deviations should be recorded and investigated, and appropriate corrective measures should be taken.	L

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		comments to lines 883-885.		
6.2.2	382-386	Requirements of Annex 13 do apply. While it may be acceptable for records limited to information of relevance to activities in respective locations to be under the oversight of "local" QPs, the comprehensive review of the manufacturing steps in their entirety against the product specification should be ensured by the QP releasing the final product.	Add wording from Annex 13.	L
6.2.2	385		Change 'files' to 'records':	L
6.2.2	388	Excipients aren't mentioned.	Add "**excipients**"	L
6.2.2	394	This list is referring to supplier's and manufacturer's information	**Supplier's**/manufacturer's batch or reference number	L
6.2.2	411	Better wording than 'special problems'?		L
6.2.2	415/416	Many starting materials are of human origin. Therefore, it should be noted that traceability records go from the donor, through all stages of manufacture, through the product, to the patient and vice versa for autologous and allogeneic 1 donor: 1 patient products.	Add following sentence: - **traceability records from the sourcing of human starting materials through the manufacturing process and the finished product to the patient and vice versa**	L
6.4	420-425	This 'other documentation' list appears to be very short and, although it uses the word 'including', does not point to other elements.	Consider inclusion of other elements in EudraLex 4.29 – 4.31 here.	L
6.5	438	Include TEPs	For cell- based products **and tissue engineered products**, …	L
7	450	Reference to the EudraLex Volume 4, Part III guidance on 'appropriate GMP' for excipients could be a useful reference to add in here, or at least a statement about assessing the supply chain in accordance with the principles of quality risk management. This could also be addressed in a separate section on Excipients.		L

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7	450-455	It is recommends that the definitions of Raw Materials and Starting Materials be clarified and aligned with of the Ph. Eur. general chapter and included in a section on "Definitions".		L
7	455	Typo	'and cells ~~**of**~~ used as starting materials'	L
7	461/462		'cover aspects of **the procurement**, production, testing and control, **storage**, and other aspects….'	L
7	462-469	The expectation for donation, procurement or testing is critical to the quality, 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 starting materials have been procured and tested appropriately to verify the quality of their product these materials. The capabilities of the supplier should be confirmed by the manufacturer. It is suggested that the ATMP manufacturer should maintain records of the evidence that the establishments have the appropriate authorisations.	Remove last sentence (lines 466-469) and replace by following sentence: "**The ATMP manufacturer should maintain records of the evidence that blood/tissue/cell establishments used have the requisite authorisations."**	L
7	464	Propose that the sentence be modified to address compliance of the **supplier's materials** with the specifications.	"For cell- based products, **tissue engineered products and genetically modified cells**, where final sterilisation is generally … "	L
7	472/473	There should not only be clear provisions about the transfer of information, but also about record keeping at the blood and tissue establishments as well as at the manufacturing site(s). See also lines 438-441.	"clear provisions about **the record keeping at the establishment and** the transfer of information …"	L
7	481/482	Final sterilisation is also not possible for tissue-engineered products, genetically modified cells (gene therapy product).		L
7	493-	Suggest that labels should also include storage	Add to this list	L

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	499	conditions to help ensure that materials are kept appropriately.	'- storage conditions'	
7	500	Automated systems should be allowed. Use of barcode on raw material container, bulk containers, and samples would be more important.		L
7	501-506	The use of starting materials that have not been released should be exceptional and there should not be occasions when products are released before the quality of the input materials have been assured. There is reference to section 11.3.2 here, but that section only covers the situation where it has not been possible to complete all quality control tests on the product.	Two options suggested: (1) Delete this whole section so as not to create the suggestion that use of starting materials before their full approval is part of good manufacturing practice OR (2) Truncate the last sentence and delete the "unless appropriate risk mitigation measures are possible" text to leave: "In such cases, the finished product can only be released if the results of these tests are satisfactory."	L
7	511-512	This sentence is lacking in clarity. The initial processing, as defined in the tissue and cells directive, 2004/34/EC, fall under the responsibility of the tissue establishment and not under the responsibility of the ATMP manufacturer. Actually, in some cases the tissues and cells are procured prior to having a particular ATMP in mind or even the intention to manufacture an ATMP in the future (e.g., embryonic and other stem cells). However, the ATMP manufacturer is responsible for defining the quality standards of the starting material when it enters the manufacturing site (i.e., "incoming goods" testing/qualification). Hence, it is encouraged the ATMP manufacturer	"The initial processing of starting material **beyond** donation, procurement and testing of tissues & cells and blood derived cells, which are governed by Directive 2004/23/EC[2], as amended, and Directive, 2002/98/EC[4], respectively, has to take place in accordance with GMP rules, even if ….."	L

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9.1	571	Improvement of wording – delete 'It is recalled that'	"Changes to the manufacturing requirements..."	L
9.1	573	Redundant 'that'	"and substantial modifications..."	L
9.1	578/579	Explicitly allow changes to the control strategy based on new information.	Additional 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."**	L
9.1	580	It is suggested to add "process monitoring tests".	"Any in-process controls, **process monitoring tests** and environmental controls should be…."	L
9.3	618	The word "should" implies a recommendation rather than a requirement. A material can be dedicated for a particular product, intermediate or a manufacturing step but not necessarily autologous.	Change the sentence to: "Mix-ups of dedicated **and/or** ~~(~~autologous~~)~~ materials **must** ~~should~~ be prevented."	L
9.3	655/656	Not only the organism should be taken into consideration to qualify the decontamination measures, but also the origin of biological raw and starting materials. A human derived starting material could e.g., be contaminated with H.I.V. or other communicable diseases.	"…taking into consideration the organism used in production **and the origin of biological raw and starting materials."**	
10	716		Replace the term "**media fill**" with "**aseptic process validation**" to distinguish from standard Fill/Finish processing of steriles.	L
10	717-719	It is not clear what is meant by "development phase". Maybe pre-clinical phase is meant.	"Manufacturing processes…… especially during pre-clinical and early clinical development phases."	L
10	719-721	It is suggested to provide some examples, e.g.: replacement of raw materials of biological origin by chemically defined raw materials; introduction of automated steps; decrease the number of handlings		L

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10	725	Delete 'It is recalled that'	"Changes to the manufacturing requirements..."	L
11.1	732/733	Clarity is required regarding what is considered to be an 'authorised site'. In certain circumstances, it may be appropriate for this to include patient treatment sites.		L
11.2	753-774	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 information is consolidated and available to the QPs for a comprehensive review.		L
11.2	768	Use of 'must'; change to 'should'	QPs should have detailed knowledge..."	L
11.3.1 (i)	799/800	In addition, the specifications of raw materials need to be verified.	- the source and specifications of starting materials, raw materials and packaging materials …	L
11.3.1 (i)	802/803	Matrixes and devices are part of the combined product.	- the excipients used in the manufacture of the finished product (including matrixes or devices that are a component of the **combined** ATMP), …..	L
11.3.1 (i)	807	In early development, devices/scaffolds/matrixes are not validated but qualified as being adequate for the use in the combined ATMP.	- **are qualified (early clinical development) or** validated **(prior to MAA)** as being adequate….	L
11.3.1 (ii)	836-838	The requirements for 'a register or equivalent document' are loose enough not to need to exempt investigational ATMPs from these requirements given that the certifications must be made available anyway. This wording also contradicts the proposed wording of the Delegated Act on GMP for IMPs which does require 'a register or equivalent document'.	Delete this sentence	L
11.3.2	871	"…where out of specification test results…"	Change to "…where **confirmed** out of specification	L

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			test results…"	
12.1	903	Minor wording change proposal since a person is being referred to	Change 'it assumes' to 'they assume'	L
12.1 (iii)	907/908		"Control of raw materials, starting materials, packaging materials, **excipients**, **devices/scaffolds/matrixes, active substances**, intermediate, bulk and…."	L
12.1 (iv)	912	Qualification (verification) or validation, as appropriate for the intended use of the method and the phase of development	Ensuring that the appropriate **qualifications and/or** validations are done.	L
12.2	928	Minor typo – it is samples that are kept, not sampling.	'Sampling' should be 'Samples'	L
12.2	935	The use of 'etc.' is not helpful guidance as it leaves too much open to interpretation.	Use the list in current EudraLex Volume 4, 6.11 here	L
12.2	936	It should be clarified that the containers being referred to here are the sample containers	"**Sample** containers should bear..."	L
12.2	944	Retention for duration of shelf-life of the product only? Would have expected this to be at least a year after the expiry date of the finished product.	Suggest "...retained for one year past the expiry date of the finished product concerned."	L
12.3	950-999	Out of specification handling may need a RBA in case limited re-testing options are available, due to lack of retain samples. It is suggested to include some wording around OOS/OOT handling in this section.		L
12.3	983	What is exactly meant by "quality attribute or as critical"? It is suggested to use the ICH terms: critical quality attribute (CQA) and critical process parameter (CPP). Since the criticality of parameters and processes are often not known in early clinical development, it is suggested to monitor the presumptive parameters and processes early on.	"Results of **attributes and parameters identified as (presumptive) critical quality attribute and as (presumptive) critical process parameter, respectively**, should be….."	L

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12.4	1001/ 1002	It is not clear whether this pre-established program is solely an internal matter for the manufacturer or whether this program has to be agreed with regulators, either as part of MAA or separately.	Clarify this point	L
13.2	1014 - 1017	If outsourcing, the contract giver may not be 'the manufacturer' and the contract acceptor may not be a subcontractor – they may be the primary contractor,	Suggest: "Prior to outsourcing any activity, the ~~**manufacturer (**~~"contract giver"~~**)**~~ should assess the suitability of the ~~**subcontractor (**~~"contract acceptor"~~**)**~~ to carry out the ~~**sub**~~contracted activities..."	L
13.2	1018/ 1019	This text may not be appropriate, depending on the activities contracted.	Suggest: "The contract giver should provide the contract acceptor with the detailed information necessary to carry out the contracted operations correctly."	L
13.2	1020/ 1021	This is guideline, so 'must' should be changed to 'should'. The inclusion of 'analytical results' creates a greater level of specificity than in necessary.	Suggest: "The contract giver **should** review and assess the records and **any results** related to the outsourced activities."	L
13.3	1024 and 1028	'subcontracted' should be 'contracted' (subcontracting is contracting to another a task that has first been contracted to you and, per 1032, is not generally acceptable).	Correct	L
13.3	1033	Wording improvement suggested	"The contract acceptor should permit ~~**the**~~ inspections ~~**of**~~ **by** the contract giver in connection with the ~~**sub**~~contracted activities."	L
14	1035	The section heading does not include the word 'Complaints' (Not all complaints are quality defects and not all quality defects are identified via complaints)	Suggest: "**Complaints,** quality defects and product recalls"	L
14.1	1046	The statement that "The authorities should be informed in accordance with the relevant regulations" is vague.	For clarity, suggest specific reference is made to the relevant regulations.	L