Submission of Comments on the Consultation Document: Good Manufacturing Practice for Advanced Therapy Medicinal Products – 26th September 2016

Comments from:

Name of organisation or individual
Cell and Gene Therapy Catapult The Cell and Gene Therapy Catapult was established in 2012 as an independent centre of excellence to advance the growth of the UK cell and gene therapy industry, by bridging the gap between scientific research and full-scale commercialisation. With more than 100 employees focusing on cell and gene therapy technologies, we work with our partners in academia and industry to ensure these life-changing therapies can be developed for use in health services throughout the world. We offer leading-edge capability, technology and innovation to enable companies to take products into clinical trials and provide clinical, process development, manufacturing, regulatory, health economics and market access expertise. The Cell and Gene Therapy Catapult is a trading name of Cell Therapy Catapult Ltd and works with Innovate UK. For more information go to ct.catapult.org.uk or visit www.gov.uk/innovate-uk.

1. General comments

General comments	
Incorporation of GMP for ATMP in the "The rules governing medicinal products in the European Union"	We commend the Commission for their efforts to provide additional guidance to the developers of ATMP. We agree this additional guidance is required and we believe developers, particularly those less experienced in the development of ATMP, would welcome greater clarity in specific points related to the manufacture of ATMP. That said, we firmly believe this document, by reproducing some but not all of Eudralex Volume 4 (Volume 4), fails to provide the specific and targeted guidance required by the developers of ATMPs. As a result, we reiterate our previous recommendation that the targeted guidance this document aims to provide on the GMP requirements for ATMPs would be best incorporated into an Annex of Volume 4, similar to what was done for the blood derived products in Annex 14, Investigational medicinal products in Annex 13, for instance. This would enable the text to focus only on the GMP elements that need adaptations to ATMPs and specifically the particularities of the individual product types (TEP, GTMP). This approach would allow focusing on the singularities of ATMPs, leaving untouched the requirements that are common to all medicinal products for human use. Volume 4 Annex 14 specifically does this for blood and plasma derived products. 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. Furthermore, we urge the commission to rethink releasing this as a standalone document for the following reasons: 1) Key components from Volume 4 are missing. Since many hospitals/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. 2) A repetition of much of Volume 4 not only lead to unnecessary duplication of work but would require repeated review and, most likely, revisions of this stand-alone document as Volume 4 (chapters and annexes) are revised. This would not be required if the document were an annex to Volume 4A. 3) A perceived divergence of quality standards over time may arise from global pharmaceutical GMP expectations which could be detrimental to the field

General comments	
	4) 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. 5) The standalone document will be less evident to developers from outwith the EU. 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. Alternatively, a further consultation could take place that specifically target 1) GMP inspectorates in the various member states and 2) companies who produce both ATMP and standard pharmaceutical products and industry representatives such as ARM, EBE-EPFIA.
Additional guidance we believe will be helpful for developers	It is recommended that developers would find extremely helpful if additional guidance was provided that to address specifics which are unique to ATMP but are not GMP issues, such as the application of the risk based approach for the inclusion of data in MAA; the categorisation of materials into Active substance, excipient, drug substance etc., environmental guidance for GMO .
Lack of clarity on what constitutes and ATMP	The guideline needs to acknowledge that at the time a sponsor wishes to manufacture an ATMP for a clinical trial it may not be obvious that a product is in fact an ATMP. Since the classification process is voluntary, and may be ongoing at the same time that CTAs are being filed, the guideline should speak to the fact that the most stringent GMP requirements possible for the product and the stage of development should be applied. It would not help a company to risk assess their GMP activities on the assumption that their product will be classified as an ATMP and later find that it does not meet the definition. Not every product that applies to CAT for ATMP classification is confirmed as an ATMP.

General comments	
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.
Format	We suggest a clear and defined Scope and Principles are added to the introduction of this document this should clearly define the following 1) The scope of the document, for example the document often discusses broader overarching Quality Management requirements and principles and CMC issues rather than the narrower scope of GMP 2) The aim of the document and the legal position for the document, if this is to remain a standalone document 3) Clarity on the Quality standard to be achieved for example this document refers to a *Pharmaceutical Quality System* where as ICH Q10 specifies that a suitable quality standard should be used and this could be a GMP based QMS or could, for example, be EN ISO based. We suggest examples could be better incorporated into a Q&A document which could be easily updates as the field evolves. A glossary of terms, for example what constitutes and active substance, drug substance etc. for these product types, would be extremely helpful. Please note that the specific comments in the text below are made on the premises that this document as a 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.

Process and next steps	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. Alternatively, a further consultation could take place that specifically target 1) GMP inspectorates in the various member states and 2) companies who produce both ATMP and standard pharmaceutical products and industry representatives such as ARM, BIA, EBE-EPFIA.

2. Specific comments on text (only contains new comments)

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')*
1. Introduction (lines 101-143)	**General** The text does not include some key GMP related documents for example product recalls handling and notification. This would be remedied by referencing Volume 4 fully or incorporation to Volume 4 as an annex. We would suggest that the Term ATIMP is adopted since this is industry norm. **Specifics** Line 109 Typo – 'is' should be replaced by 'are' Lines 137-143 This paragraph is extremely unclear. Suggested wording: A Pharmaceutical Quality System should be in place for the entire product life cycle (ICH Q10) and products (ATIMP and marketed ATMP) should be manufactured and released under the auspices of GMP.

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2. Risk-based approach (lines 144-341)	**General** As discussed above we believe it is important to prevent the confusion and divergence of quality standards both for ATMP as a group of product but also for manufacturers who manufacture both product types. It is suggested that the term Risk Based approach is replaced by Quality Risk Management (as per ICH Q10), as per Eudralex Volume 4. However, it would be useful to add in section 2.1. making 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). There needs to be a statement that explicitly allows changes to the control strategy based on new information. Proposed change (if any): 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." **Specifics** **Line 182** Spelling: Matrices **Line 206 - 225** The Pharmaceutical quality system is not examined in detail by pharmaceutical assessors, rather they assess the outputs from the system and the robustness of the data therefrom. It is instead Medicinal Product inspectors who assess the appropriateness of the QMS for the stage of development of the product, as such the application of the QRM principle will need to be justified in internal processes and documentation and be available for inspection. It is suggested the explanation

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	of these paragraphs is expanded to include further explanation of the requirements for GMP verification and documentation vs that required as part of a dossier submission **Lines 236 – 239 – Qualification of suppliers of raw materials** • It is not necessarily the case that raw material interaction with starting material would constitute a higher risk, if this is to be included further explanation would be beneficial • The guidance needs expanded since qualification of suppliers is one part of this control strategy. • Reference to Ph.Eur. monograph 5.2.12 should be included • Lines 240-241: "Qualification of suppliers" should be defined and clearly delineated from "outsourced activities" (13.). ○ In particular, the obligation for raw material manufacturers with regards to change control should be delineated from those claimed for contract acceptors in 13.3, line 2015-2017. As an example, see our proposal hereafter (modifications to 13.3, line 2015-2017 underlined): "The raw material supplier should notify the ATMP manufacturer of any relevant change, affecting safety or specifications of the raw material, in writing, prior to planned implementation for any production or release of any lot made after the change". **Line 244** The use of the term *active substance* is often confused by ATMP developers as per our request above we suggest a glossary is added which could provide guidance on this. **Line 246** – Spelling – immediately **Line 267** It is suspected some words have been lost

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')*
	Lines 284 – 292 We suggest a rewording to incorporate…. The level of qualification /validation should be commensurate with risk and the stage of product development. **Lines 293 –302** In general, Annexes1 and 2 discuss the aseptic requirements in more detail and we believe these documents should remain the core documents for this subject matter. These documents already allow for a risk based assessment of the stringency for aseptic processing. Specific points • The text needs to clarify that aseptic processing will not be required if the developers are operating a closed system. • The text implies rooms operate to Grade A, this is incorrect, aseptic Grade A zones will be area within Grade B cleanrooms (this comment relates to a number of entries in the document). **Lines 303 – 313.** We suggest the topics raised here are better covered by a section on Scope in the introduction. **Lines 315 -319** It is suggested that equipment validation/qualification rather than equipment calibration is the appropriate term. ***Section 2.3.4 Additional considerations…..*** We reiterated that a risk based approach is already in place for the manufacture of medicinal products (investigational and marketed products). As set out in ICH Q10, this should be commensurate with the predetermined risk for the product and

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	the recipient of the product. As a consequence, with patient/trial subject safety in mind, we suggest that the guidance should emphasise that a reduction in standards during aseptic processing would not be acceptable however other deviations might be acceptable if following risk assessment, they were appropriately justified. It is important to reinforce flexibilities would only be permissible if the manufacturing and release strategy required this to allow supply the product and that the potential benefits outweigh the risk of this approach **Specifics** **Lines 328 – 333** . It is suggested that if equipment is shared between processes then greater verification and ppm oversight may be required. The cycle of verification and maintenance should be set per piece of equipment and process should be set following appropriate risk assessment and justification.
3. Personnel	The text incorporates a lot of Volume 4 we suggest an annex discussing specifics such as vaccination would be more helpful. **Lines 352 – 357** The text implies that all staff employed in the production of ATMP should be trained in aseptic processes and best practices. This should be amended to explicitly state this is required for staff operating in a cleanroom. **Line 365 -366** It is unclear why there is a need to state training can be in-house since as this is standard practice.

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')*
	Line 368 – 369 It is unclear what is meant by 'Hygiene Programs should be established'. More guidance should be given
	lines 411-418 Additional guidance on vaccination would be useful. Should all personnel receive Hepatitis B vaccine? The risk to personnel resides not just with the product but with some of the materials used in production. As some personnel handle the materials but not the products, it is important to highlight both risks. Proposed change: Add to the end of the last sentence in the paragraph, 'and the materials used in its production.'
4. Premises	**General** The text incorporates a good deal from Volume 4, but crucially omits some critical information, we suggest an annex discussing specifics for ATMP such as a sample receipt area for human starting materials etc. would be more helpful. **Specifics**
4.2. Production areas	The guideline should take the complexity of ATMPs into account to a greater extent, or provide clarification. Section 4.2 states that the manufacture of ATMPs should take place in a dedicated area of the facility, but this does not account for

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	the fact that ATMPs can be more dissimilar and pose more risks to another ATMP that they do to a different type of product. For example, per the guideline it would be OK to make an ATMP based on human cells in the same area as a device that used engineered CHO cells in a device matrix, if they are both classified as ATMPs, but an antibody growing in CHO cells would have to be manufactured in a different area.
4.2.1. Design and construction	There is not a clear description of Air locks and pass through with pressure differential, interlocks and timing when doors can be open
4.2.2 Aseptic environment	It is disputed that a Grade D environment is required for a fully closed system. Controlled non classified should be sufficient, for example Blood Services who employ many 100,000s closed system processes each year are not required to operate to grade D conditions Also the risk of the process and the design of the isolator may need to be considered before it can be assumed that grade D is acceptable **Lines 512-513** Suggest Monitoring *of isolators……*is added to the text **Lines 527 – 530** Particles >5µM are omitted from the text here but are discussed later in the document (Lines 559 -560). If this is not an omission can the rational for not monitoring nonviable particulates at this size be provided since a rise in these particulates can often indicate a problem with the environment e.g. may indicate a problem with HVAC
5. Equipment	No additional comments to those listed in the general section.

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6. Documentation	It is suggested that more emphasis is provided on the need to maintain Traceability and guidance provided to manufacturers on how to meet this obligation
6.1 Documentation	It is not clear from this section if the document is referring to key QMS documentation (e.g. contracts) or key GMP documentation. Chapter 4 of volume 4 refers to 2 primary document types involved in GMP operations - instructions and reports
6.2. Specifications and instructions	Reference is made to the potential for non-substantial and substantial amendments (modifications) to be filed to the IMPD. However, the Regulation quoted does not provide guidance on what would be considered substantial and non-substantial for ATMPs. Since we know that the list of substantial amendments in the EMA guideline for biological products for clinical use (EMA/CHMP/BWP/534898/2008) is different from that in the EMA guideline for APIs (CHMP/QWP/185401/2004), it would follow that the list could be different again for ATMPs. Without that guidance Competent Authorities are likely to have different expectations for modifications requiring prior approval. Industry should encourage the development of this list in parallel to this GMPs guidance, or the sections on amendments will be hard to apply in the context of ATMPs.
	Lines 765 – 766 The should be included to include directed allogeneic batch **Line 838** Since ICH Q2 stability programmes are not suitable for many cell based and Tissue engineered products, we would suggest that guidance on possible stability testing strategies would be useful to developers.

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	Lines 841- 855 A number of key documents required for compliance with ICH Q10 which are included in Volume 4 are omitted from the list of key records/reports. e.g. • Change controls • Validation of systems/processes • Audits • Complaints • Product defects
6.5. Retention of documents	
	Lines 885 – 888 Whilst the text is correct in quoting what the Regulation states we suggest the guidance should be broadened to explain the requirement for the retention of data only on raw materials which could potentially affect the quality and /or safety of the product
	Lines 910 – 911 The use of the term donor is incorrect in relation to xenogeneic cells
7. Starting and raw materials	

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')*
7.2. Raw materials	The section should clarify that the products need to be assessed for suitability to ensure they are fit for the intended purpose. The fact that raw materials that are approved for use as medicinal products themselves do not require CoAs (Section 7.2) is helpful, but it is not clear if the products need to be approved in the EU for this to apply, or if a material approved anywhere meets this requirement. There is an implication that some proof of approval or other reference to the quality of the material will be provided in order to justify the omission of the CoA, but the guideline does not explicitly state what should be provided. This should be clarified. line 936-937: add underlined words: "While raw materials should be of pharmaceutical grade or other grades with documented adherence to relevant GMP principles and safety standards, it is acknowledged …" In addition, it is suggested that reference is made to Quality Risk Management principles here.
	line 940-942: Suggested rewording: "Additionally, the manufacturer of ATMP should ensure the suitability of such raw materials for the intended use, including, where appropriate, by means of testing (e.g. functional and/or safety test)".
7.3 Starting materials	ARM understands that the Tissues and Cells and Blood Directives have not been uniformly transposed into member state law and as such there are different interpretations and enforcement with regard the activities over an above Donation, Procurement and Testing for material used as Starting Materials as such the guidance provided here may be contradictory to that in national member state law.

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	In addition, the definition of starting material/critical raw material/active substance is often confused by developers and regulators, for example in the case of viral vectors. We recommend this is exactly the type of specific guidance required in this guidance document should provide guidance on this which can be incorporated into Volume 2 NTA. **Line 982** Since some products may be considered to be derived from blood rather than Tissues and Cells we suggest that reference should also be made to the Blood Directive 2002/98/EC
8. Seed lot and cell bank system	**General** We recommend specific guidance is provided in this document should provide more structured guidance relevant to developers related to the QC testing requirements such as identity testing, minimal viral risk testing algorithms etc. and comparability requirements following batch replacement **Lines 1070 – 1072** However, the establishment of seed lots/cell banks is not mandatory *[Add] or may not be appropriate*.
Lines 1117-1119	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. **Proposed change (if any):** 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

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')*
	Lines 1126-1129 Suggest rewording to : A risk analysis should be conducted to identify *any gaps in the information that would be required to meet current day GMP standards e.g. donor consent, donor testing etc. and to detail mitigation to any identified areas where this is reduced or missing information* **Lines 1159-1162** 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 person/department responsible for quality control when appropriate. *Suggest rewording to* Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be fully investigated and assessed for the potential impact on product and environment and if appropriate, approved in writing by the person responsible for manufacturing, with the involvement of the person/department responsible for quality control when appropriate. **Lines 1161, 1177, 1423, 1428** Quality Control is used incorrectly here and in the remainder of the document, this should be replaced by Quality Assurance unless the text is specifically related to testing of quality parameters

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9. Production	Once more of this section incorporates some but not all of Volume 4 we suggest an annex discussing specifics of the production of ATMP would be more helpful.
9.3.1 Water	This production of pharmaceutical grade water is a high risk activity and it is suggested that more guidance is required for users who are less familiar with or who have no knowledge of the production, testing and maintenance of this utility. The paragraph needs to be expanded greatly and with reference to relevant EP manographs etc.
9.3.3. Clean Steam	This is a high risk activity and we would suggest that more guidance is required for user who are unfamiliar with the use of this utility
9.4. Prevention of cross-contamination	It is suggested that the need for appropriate line clearance (product and labelling) is included in this section of the guidance. In addition, the highest risk to product contamination is personnel based. We suggest more guidance is provided for personnel moving between areas within the same facility.
	Lines 1242 – 1246 Cleaning would be required between batches irrespective of whether the product was autologous or allogeneic. **Lines 1267 – 1274** A closed system normally related to the manufacturing processing plastic ware and equipment rather than containment equipment such as isolators and as such the use of the phrase may be confusing in this context Guidance should also be provided for the use of MSC which are often used rather than isolators in processing of ATMP **Lines 1283 – 1289**

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')*
	This paragraphs should be expanded to provide more detailed guidance
9.5. Aseptic manufacturing (Lines 1332-1336)	**General** It is suggested this section lacks the detail of Volume 4, annexes 1 and 2 and should be expanded. For manual aseptic manufacturing processes where every patient dose is tested for sterility as part of lot release, is the conventional concept of aseptic validation appropriate/required? Ep Monographs 2.6.1 (Sterility) and 2.6.27 (Microbial Examination of cell-based Preparations) should be referenced and detail provided on the appropriate use of these monographs
	Process Simulation Tests (PST) For some products, sterility test results for each individual produced dose, will be available at lot release and the material will have already been used by the patient; while an investigation can be conducted, product impact will already have been established during lot release.
	For manual aseptic processes, it is important to ensure that every operator is qualified to perform all aseptic operations successfully; in addition to confirming that the process itself (process, materials, facility, personnel combined) can be validated for aseptic performance. The requirement to include "each shift" could also be met by having operators perform 3 consecutive qualification exercises (process simulations) on select aseptic operations.

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')*
	Is it possible to consider aseptic control strategies that include an aseptic operator qualification program incorporating process simulations, environmental and personnel monitoring, and sterility testing of each individual patient dose, in lieu of mandatory time-based media fills? Failure of control strategies would trigger media fills if warranted.
	Lines 1339 -1345 It is important that a Process Simulation Test (PST) should include known possible interventions and possible worst case situations, we suggest such detail guidance, as provided in Volume 4, is provided by this guidance. **Line 1355** PST is a media fill. We would propose that *'with media fill test'* is removed **Lines 1365 – 1367** We would suggest that the PST process and frequency should be stated to be based on risk, irrespective of the intended use of the product
9.7. Packaging	IT is requested this document produces more guidance on the specifics of labelling of ATMP e.g. labelling of product for storage at ultralow temperatures, small package sizes, the provision of an aseptic primary container etc. The requirements for primary packaging for ATMPs appear more stringent than those for conventional product, specifically the requirement for "approval and maintenance" of the suppliers of these materials. The wording suggests that the suppliers of primary packaging for ATMPs are subject to a degree of scrutiny greater than suppliers of packaging for conventional products. Since suppliers may not be prepared to undergo additional scrutiny for clients seeking to register low volume products this requirement has the potential to adversely affect ATMP manufacturers.

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	The reference to validation of the closure (line 1396) is also unclear. Is the reference to the performance of container closure integrity testing, or is there an expectation that a specific torqueing process will be used and validated?
10. Qualification and validation	This section lacks a lot of detail and more is required for example in operation and at rest parameters etc., reference should be made to the detail contained in Volume 4 In several places (Section 2.3.4, line 239; Section 10.2, line 1548) the guideline makes the assumption that when few batches are made, a less stringent approach to GMP can be taken. It would be helpful if the guideline could provide more information on how that conclusion has been reached. Issues with equipment calibration will be much harder to detect when very small numbers of batches are manufactured, since no trending can be performed, and specialized equipment could be stored for long periods without use. A pragmatic approach would be to propose an as needed calibration program for very low volume products. **Line 1459** As per earlier comment, Cleanrooms are Grade B, but may contain Grade A zones, suggest this is changed to grade A zones .

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')*
10.2. Cleaning validation	The cleaning verification requirements for investigational products are unclear, since they depend on the volume of production. If the volume of production is small (less than 3 batches) then verification alone is considered sufficient. Cleaning verification, as opposed to cleaning validation, is not defined in the guideline. In addition, no context is provided for the production volume (is this less than 3 batches a year, a campaign, ever? Etc.) It is unclear how the number of batches of the ATMP affects the extent to which those batches could be contaminated with another product, since for low volume products the previous batch is more likely to be a different product, and hence the risk of cross-product contamination greater on a batch by batch basis. **Line 1535** Validated methods that should be sufficiently sensitive to detect residue levels **Line 1564** This does not include all of the parameters required by Annex 15 for clear guidance this section should be expanded in line with this annex
10.3 Process validation	The flexibility introduced in this section s welcomed and this guidance is what is required for inexperienced developers, however it is unclear if the sections included from line 1587 are definitions or if these processes are permissible for ATMP. If this is the case then we suggest more guidance on when these are applicable are required especially for circumstances such as concurrent validation which is generally unacceptable to CA, in particular if surrogate material is being used in this concurrent validation. **Spelling 1602** – ratio

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')*
	Line 1623 Investigational ATMPs Suggest change to : It is expected however that the aseptic conditions of the manufacturing process have been validated.
11. Qualified person and batch release	**Lines 1658 -1663** Suggest this is expanded to include: The QP should also understand and take into account the requirements of the Blood Directive (2002/98/EC) and the Tissue and cell directive (2004/23/EC) **Lines 1667 – 1668** This should state EU GMP **Line 1676** A clear definition of the active substance should be provided.
Section 11.3.1	Provide clarification on whether this is batch release or certification.
Section 11.4	The discretion proposed is not permissible according to current legislation which requires the QP to certify against registered procedures with no discretion by the QP. A change to the legislation is required to effect this.

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12. Quality control	The functions of QA and QC are becoming confused and should be disentangled and explained fully
12.2 Sampling	It is requested that this document should provide more guidance on specifics for ATMP
	Lines 1911- 1916 It is suggested this text is reviewed; for example, a ATMP could have a shelf-life of say 28 days where as a classic pharmaceutical have a shelf-life of 3 years. It is suggested that this retention period should l be risk based and based on the product characteristics rather than a direct translation form the current volume 4 as per the flexibility detailed below **Lines 1919 – 1927** Guidance should be provided on the usefulness of samples retained in other media such as formaldehyde or wax embedded sections for products such as TEP **Lines 1958 – 1960** it is unclear why this is called out here whereas tech transfer of processing methods is not discussed. It is suggested that tech transfer in entirety should be covered in a separate section
12.4. Stability monitoring programme	Section 12.4 states that the stability program should be implemented after the MAA is granted (line 1972), but the stability program should be established prior to the MAA, so that the stability protocol becomes part of the regulatory commitment. Stability data is however needed early in development both for regulatory submissions and to ensure the quality of the product. Guidance on stability trial requirements would be welcomed by developers.

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13. Outsourced activities	
13.3. Obligations of the contract acceptor	"Qualification of suppliers" should be defined and clearly delineated from "outsourced activities" (13.). In particular, the obligation for raw material manufacturers with regards to change control should be delineated from those claimed for contract acceptors in 13.3, line 2015-2017. As an example, see our proposal hereafter (modifications to 13.3, line 2015-2017 underlined): "The raw material supplier should notify the ATMP manufacturer of any relevant change, affecting safety or specifications of the raw material, in writing, prior to planned implementation for any production or release of any lot made after the change".
15. Environmental control measures for ATMPs containing or consisting of GMO's	It is suggested, in order to provide GMP guidance, this section should focus on facility control measures rather environmental. In general, more guidance on the specifics for the manufacture, testing and stability studies for Gene Therapy and Tissue-Engineered products should be provided in this document.
16. Reconstitution of product after batch release	**General** Guidance should be provided on the handover of responsibility between the manufacturer of the ATM and the clinical site taking on responsibility for Preparation steps. The guidance should specifically state the preparation must be in compliance with that included in the MAA or CTA and instructions provided by the manufacturer to the clinical site. It is suggested the term 'Reconstitution' is replaced by 'Preparation' because this will be clearer and avoid confusion.

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')*
	Whilst it is acknowledged these steps are often required for ATMP products and it is suggested that specific guidance on issues such as this should be provided in this document rather than a reiteration of volume 4. Lines 2097 -2101 *The above steps can only be part of the reconstitution process if it is appropriately justified that these steps cannot be performed as part of the manufacturing process before QP release without negative impact on the product. Additionally, the above activities can only be considered "reconstitution" when they are carried out at administration site (i.e. it is not acceptable to have these steps outsourced to a third party that is not GMP-compliant).* We suggest that the guidance should acknowledge that hospital units may use a shared pharmacies or cell labs to perform this function which although not a CMO could be considered as third party and as such should be considered to be part of the administration site
17. Automated production of ATMPs	We welcome that the commission has addressed this area in the guidance. However, it raises many complex regulatory and legislative issues which are unique to automation and distributed manufacture. We suggest this may be better served in a separate guidance document.