Submission of Comments on the Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

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Comments from:

Name of organisation or individual
Novadip Biosciences (NVD) Watson & Crick Hill Rue Granbonpré 11 1435 Mont-Saint-Guibert - Belgium Email: info@novadip.com Size/Type of enterprise: Micro/Autonomous EMA-SME number : EMA/SME/488/15 Novadip Biosciences is a biopharmaceutical company that pioneers the growth of 3-dimensional tissues derived from adipose stem cells to regenerate bone and soft tissues.

1. General comments

General comments	
Incorporation of GMP for ATMP in the "The rules governing medicinal products in the European Union"	We welcome the aim of this document to provide specific guidance for developers of ATMP. The new Consultation Document has been significantly expanded compared to last year Consultation Document. Our main recommendation is to design the document as an Annex to the EudraLex Volume 4 of the "The rules governing medicinal products in the European Union" rather than as a separate, stand-alone document. NVD firmly believes this document, by reproducing some but not all of Eudralex Volume 4, fails to provide the specific and targeted guidance required by the developers of ATMPs. Our recommendation is that GMP requirements for ATMPs is incorporated into an Annex of Volume 4, similar to what was done for the blood derived products in Annex 14 or for Investigational medicinal products in Annex 13, for instance. This would enable the text to focus only on the GMP elements that need specific adaptations for ATMPs taking into account the particularities of the individual product types (TEP, GTMP), with clear cross-referencing to other requirements that are common to all medicinal products for human use. This approach would add clarity and visibility as it would only deal with the specific elements for ATMPs and it would serve its purpose to act as a comprehensive reference document for all ATMP manufacturers. Subsequent revisions will also be much simplified as these would be limited to changes required due to progress in the field of ATMPs. Volume 4 Annex 14 specifically does this for blood and plasma derived products. NVD urges the Commission to rethink releasing this as a stand-alone document for the following reasons: 1) Key components from Volume 4 are missing, such as for instance product recall handling and notification. 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 resulting in different quality standards;

General comments	
	2) A repetition of much of Volume 4 not only leads to unnecessary duplication of work but would require repeated revisions. Indeed, experience shows that the updating of chapters and Annexes in Volume 4 are very frequent meaning that a stand-alone document for ATMPs that duplicates requirements of these chapters and Annexes would be in constant revision. This would not be required if the document were an annex to Volume 4A; **3) A divergence of quality standards CANNOT arise from 'regular' pharmaceutical GMP expectations and would be detrimental to the safeguard of public health;** 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 stand-alone document will be less evident to developers outside the EU.
Risk-based approach and other useful examples	We believe that the elements pertaining to a risk-based approach in the context of GMP should be more clearly differentiated from those to define the appropriate standards of data in a clinical trial or marketing authorisation. It would be useful to review the examples provided in section 2 "Risk based approach" with this in mind. Additional information on the categorisation of materials into Active Substance, Drug Substance, excipient, etc, and on GMO environmental control for GMO's, with examples, would also be extremely useful (see also comment below on 'Format and other useful guidance').
Lack of clarity on the ATMP status	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	**NVD believes that 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.
Format and other useful guidance	We suggest sections on Scope and Principles are added to the introduction of this document to clearly define the following elements: 1) The scope of the document; for example, the consultation document often discusses broader overarching Quality Management requirements and principles and CMC issues rather than the narrower scope of GMP; 2) The aim and the legal position for the document, if this is to remain a stand-alone 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 updated as the field evolves. A glossary of terms, for example to define what constitutes and active substance, drug substance etc. for these product types, would be extremely helpful.

General comments	
	Please note that the specific comments in the text below are made on the premises that this document is 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 stand-alone 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, NVD asks for the guidance document to be approved by the Inspectors Working Group prior to finalisation.** NVD is convinced of the value of such meeting and would like to reiterate its request for an interactive meeting grouping together ATMP manufacturers, the Inspectorate Working Group, the EMA and the European Commission before finalisation of the document.

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

Section in the Consultation Document	Comment and rationale; proposed changes
1. Introduction	
General:	The text does not include some key GMP related documents such as for example, product recalls handling and notification. This would be remedied by referencing Volume 4 fully or by incorporating it to Volume 4 as an annex.
Line 109:	Typographical error: 'is' should be replaced by 'are'.
Lines 135-136:	We would suggest that the Term ATIMP is adopted rather than investigational ATMP since this is the term used in all other relevant regulatory documents.
Lines 137-143:	This paragraph is extremely unclear because GMP and the risk-based approach for GMP standards should be clearly distinguished from regulatory requirements for marketing or clinical trials authorisations. Proposed change: '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.'

Section in the Consultation Document	Comment and rationale; proposed changes
2. Risk-based approach 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 products but also for manufacturers who manufacture both ATMP and other medicinal products. 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. a 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. It is proposed to add a 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." Typographical error 'Matrixes' should be replaced by 'Matrices'.
Line 182:	

Section in the Consultation Document	Comment and rationale; proposed changes
Line 206 – 225:	The Pharmaceutical quality system is not examined in detail by pharmaceutical assessors, rather they assess the ouptuts 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 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 238 – 239:	It is not necessarily the case that raw material interaction with starting material would constitute a higher risk; Proposed change: remove the text in brackets or alternatively, provide additional explanation with an example.
Lines 240-241:	The guidance needs to be expanded since qualification of suppliers is only one part of this control strategy. Alternatively 'i.e. qualification of suppliers' should be changed into 'e.g. qualification of suppliers' "Qualification of suppliers" should be defined and clearly delineated from "outsourced activities" (Section 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

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 229-241:	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:	It is recommended that a sentence referencing Ph.Eur. chapter 5.2.12 on "Raw materials of biological origin for the production of cell-based and gene therapy medicinal products for human use" should be included
Line 246:	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 267:	Spelling mistake: replace 'immediatly' by 'immediately'
Lines 284 – 292:	It is suspected some words have been lost in this sentence. The recommendation is not clear. We suspect this paragraph refers to situations of cell-based products for non homologous use (hence their ATMP status).

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 293 –302:	Proposed change: The level of qualification /validation should be commensurate with risk and the stage of product development. The quality requirements for Tissues and cells are set out in 2004/23/EC and corresponding commissioning Directives 2006/17/EC and 2006/86/EC and corresponding national legislation of the member states. In general, Annexes 1 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.
Lines 303 – 313: Lines 315 – 319:	Additional 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 314 - 340:	We suggest the topics raised here are better covered by a section on Scope in the introduction.

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 328 – 333	It is suggested that equipment validation/qualification is a more appropriate term than equipment calibration. General comment on section 2.3.4. *'Additional considerations specifically relevant for investigational ATMPs'*: As set out in ICH Q10, a risk based approach is already in place for the manufacture of medicinal products (investigational and marketed products) and it should be commensurate with the predetermined risk for the product and the recipient of the product. As a consequence, with patient/trial subject safety in mind, we do not agree to a general lowering of standards for First-In-Man clinical trial products per se as suggested in lines 322-327; rather, any deviation from Volume 4 requirements should be following risk assessment and appropriately justified. It is important to reinforce that flexibilities would only be permissible if the manufacturing and release strategy requires this to allow supply the product and that the potential benefits outweigh the risk of this approach. It is important to note that equipment may often by shared between processes in small facilities. It is suggested that such shared equipment might require greater verification and planned preventative maintenance pm oversight rather than less and this consideration should be included in the guidance.

Section in the Consultation Document	Comment and rationale; proposed changes
3. Personnel General:	The text incorporates a lot of Volume 4 requirements; as mentioned above, rather than repeating the text from Volume 4, we suggest an annex discussing specific requirements for ATMPs referring to the appropriate sections in Volume 4 for all other aspects.
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.
Lines 365 – 366	It is unclear why there is a need to state training can be in-house since as this is standard practice.
Lines 368 – 369	It is unclear what is meant by 'Hygiene Programs should be established'. More guidance should be provided.
Lines 411 - 418	Additional guidance on vaccination would be useful, such as: 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 the following words at the end of the last sentence in the paragraph: 'Other measures may need to be put in place to protect the personnel according to the known risks of the product and the materials used in its production.'
4. Premises General:	

Section in the Consultation Document	Comment and rationale; proposed changes
	The text incorporates a good deal from EudraLex Volume 4, but omits some critical information. Our suggestion to deal with an annexe discussing specific requirements for ATMP such as a sample receipt area for human starting materials etc., would address this issue.
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 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 Lines 506 – 507:	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.

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 512 – 513: Lines 527 – 530:	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 Proposed change: "Monitoring of isolators should be carried out…" . 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.
6. Documentation General:	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 General principles	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.

Section in the Consultation Document	Comment and rationale; proposed changes
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 batch definition should also mention directed allogeneic batch. Proposed change: 'For autologous and directed allogeneic products, each unit should be considered as a distinct batch'.
6.3. Records Line 838:	It is implied here and later in the document that an examination of the stability of the product is only required for marketed ATMP. This is incorrect, moreover this is common mistake made by academic developers of ATMP. This guidance must detail that the stability of ATIMP should be examined and should recommend this is built into the early development path for the product.
6.4. Other documentation	

Section in the Consultation Document	Comment and rationale; proposed changes
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	General: Retention of Documents should include an acknowledgement that some ATMPs will have documentation storage times specified by other directives and regulations, e.g. tissues and cells directive 2004/23/EC requires data required for traceability to be stored for 30 years. This is acknowledged in the section on Traceability (6.6) but that section is also inconsistent. The guideline should start with the assumption that the manufacturer of an ATMP that uses materials subject to the requirements of 2004/23/EC, and subsequent directives, should plan to retain donor identification codes, batch records and information on critical raw materials and active substances for 30 years. The information in the guideline on batch record retention (line 870) is contradicted by the instructions on retention of the batch record for traceability (line 889) and this should be clarified in the text.
6.6. Traceability Lines 885 – 888:	Whilst the text is correct in quoting what the Regulation states, it is suggested 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.

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 910 – 911:	The use of the term donor is incorrect in relation to xenogeneic cells.
7. Starting and raw materials 7.2. Raw materials General: Lines 936 – 937: Lines 940 – 942:	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. Proposed change: "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.

Section in the Consultation Document	Comment and rationale; proposed changes
	The following rewording is proposed: "Additionally, the manufacturer 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 Line 982:	NVD understands that the Tissues and Cells and Blood Directives have not been uniformly transposed into member state law and that there are different interpretations and enforcement with regard to the activities over Donation, Procurement, Testing and Release for materials used as Starting Materials. Requirements about testing and respective responsibilities provided in this guidance may potentially be contradictory to that in national member state law. 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. Such specific guidance could be provided in this guidance document and then incorporated into Volume 2 of the Notice to Applicant. Reference should also be made to the Blood Directive 2002/98/EC.
8. Seed lot and cell bank system General:	NVD recommends 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.

Section in the Consultation Document	Comment and rationale; proposed changes
Line 1072	Proposed change: 'However, the establishment of seed lots/cell banks is not mandatory or may not be appropriate'.
Lines 1117 - 1119	The term "cell stock changes" should include introduction of new cell bank(s) obtained from new donors. Proposed change: **"**Cell stock changes and introduction of new cell banks(s) derived from new donors ~~(including introduction of cells from new donors)~~ should be addressed in the marketing authorisation and the conditions therein should be complied with."
Lines 1126 - 1129	The following rewording is proposed: "In these cases, a risk analysis should be conducted to identify any gaps in the information that would be required to meet current GMP standards e.g. donor consent, donor testing etc. and to detail mitigation to any identified areas where this is reduced or missing information ~~the testing requirements necessary to ensure the quality of the starting material~~"
9. Production General:	This section incorporates once more some but not all of Volume 4; we suggest an annex discussing specifics of the production of ATMP would be more helpful.
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.

Section in the Consultation Document	Comment and rationale; proposed changes
9.1. General principles Lines 1159-1162:	Proposed change: “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.”
9.3. Utilities 9.3.1. Water	This production of pharmaceutical grade water is a high risk activity and we would suggest that more guidance is required for user 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 provide concise advice e.g. the water system in its entirety should be fit for purpose rather guidance be limited to the pipes. Therefore, this statement should include tanks, sample points etc. with reference to relevant documents such as EP monographs.
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 in production	

Section in the Consultation Document	Comment and rationale; proposed changes
General: Lines 1242 – 1246:	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. Cleaning would be required between batches irrespective of whether the product was autologous or allogeneic. We propose to remove the words 'For autologous products'.
9.5. Aseptic manufacturing General:	It is suggested this section lacks the level of details 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 details provided on the appropriate use of these monographs. Process Simulation Tests (PST):

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 1267 – 1274:	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 selected aseptic operations. 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 1283 – 1289:	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.
Lines 1332 – 1336:	Guidance should also be provided for the use of MSC which are often used rather than isolators in processing of ATMP.
Lines 1339 – 1345:	This paragraph should be expanded to provide more detailed guidance. 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?

Section in the Consultation Document	Comment and rationale; proposed changes
Line 1355: Lines 1365 – 1367:	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. See also general comment above. PST is a media fill. We would propose that *'with media fill test'* is removed. 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 General: Lines 1395 - 1396:	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 products, 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. The reference to validation of the closure is 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?

Section in the Consultation Document	Comment and rationale; proposed changes
9.9. Rejected, recovered and returned materials Lines 1416 – 1418:	This sentence is too vague, since the word "contemplated" is not definitive. Proposed change: "For authorised ATMPs, reprocessing is only permissible if the reprocessing procedure is described in the Marketing Authorisation, the specific conditions under which it would be performed are defined, and data are presented to support it".
10. Qualification and validation General:	This section lacks a lot of details, for instance with regard to operation and at rest parameters. Reference should be made to the details 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 ad-hoc calibration program for very low volume products.

Section in the Consultation Document	Comment and rationale; proposed changes
Line 1459:	As per earlier comment, Cleanrooms are Grade B, but may contain Grade A zones. Proposed change: replace 'clean room of grade A' into 'Grade A zones'.
Lines 1486 – 1489:	It is suggested that what is proposed may introduce unnecessary risk. Can the Commission provide examples of when such concurrent validation could be justified if surrogate material is to be used for validation?
Lines 1494 – 1498:	This lacks the detail and the instruction that validation should be prospective and that protocols should be written and approved by the appropriate personnel in advance, as we believe this guidance is required for inexperienced developers.
10.2. Cleaning validation Lines 1546 – 1550:	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:	Proposed change: "Validated analytical methods that should be sufficiently sensitive to detect residue levels."
Lines 1564 - 1574:	The list does not include all of the parameters required by Annex 15; for clear guidance this section should be expanded in line with this annex.

Section in the Consultation Document	Comment and rationale; proposed changes
10.3 Process validation General:	The flexibility introduced in this section is welcomed and this guidance meets requirements 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.
Lines 1602:	Spelling mistake: change 'ration' into 'ratio'
Line 1623:	Proposed change : "~~Additionally, i~~t is expected however that the aseptic conditions of the manufacturing process have been validated."
11. Qualified person and batch release Lines 1658 -1663:	It is proposed to expand this paragraph to include reference to Blood Directive and the Tissue and Cell Directive. Proposed change: add the following sentence "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.

Section in the Consultation Document	Comment and rationale; proposed changes
Line 1676: 11.3.Batch release (lines 1714 and following): Lines 1782 – 1785:	A clear definition of the active substance should be provided. Clarity should be provided on what relates to batch release or batch certification. It is suggested that the qualification and training of this person needs to be discussed and advice provided. Furthermore, it is very difficult to understand how a QP will be able to justify a decision made by the designated person if they themselves were not involved in that decision making process. As such we believe a 2 stage certification should be performed by a QP. If however these 2 stages are to be performed be 2 different individuals, then there needs to be a technical agreement between the individuals as there currently is between QPs.
11.4. Handling of unplanned deviations	The discretion proposed in case of unplanned deviation is not permissible according to current legislation: 2001/83/EC Art. 13 , Volume 4 Annex 13 and Annex 16 requires the QP to certify against registered procedures with no discretion by the QP. A change to the legislation is required to effect this. As such this clause must be removed until the legislation is revised.

Section in the Consultation Document	Comment and rationale; proposed changes
12. Quality control General:	The functions of QA and QC are becoming confused, they should be disentangled and explained fully.
Lines 1853 – 1927: (12.2. Sampling)	More guidance on the aspects of sampling that are specific for ATMPs would be very helpful.
Lines 1911- 1916:	It is suggested this text is reviewed; for example, a ATMP could have a shelf-life of 28 days where as a classic pharmaceutical have a shelf-life of 3 years. It is suggested that this retention period should 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. Guidance should be provided on the usefulness of samples retained in other media such as formaldehyde or wax embedded sections for products such as Tissue Engineered Products.
Lines 1919 – 1927:	It is unclear why technical transfer of testing methods is called out here whereas technical transfer of processing methods is not discussed. It is suggested that technical transfer in its entirety should be covered in a separate section.
Lines 1958 – 1960:	The section 12.4. 'Stability monitoring programme' states that the stability programme should be implemented after the MAA is granted (line 1972), but the stability programme should be established prior to the MAA, so that the stability protocol becomes part of the regulatory commitment. Stability data should be generated pre-approval, ideally on lots used in the clinic, and studies should be presented to support the proposed shelf-life.

Section in the Consultation Document	Comment and rationale; proposed changes
Lines 1971 - 1989:	
13. Outsourced activities General:	"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, the following change is proposed on lines 2015-2017: "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".
14. Quality defects and product recalls General: Lines 2050 – 2051:	

Section in the Consultation Document	Comment and rationale; proposed changes
	This section should be expanded to cover the different aspects covered in EudraLex Volume 4, Chapter 8, such as handling of product recalled, notification to competent authorities, etc. The destruction of a defective product at the clinical site may require consent of the donor.
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 on environmental measures. 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 ATMP and the administration site taking on responsibility for the 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 administration site.

Section in the Consultation Document	Comment and rationale; proposed changes
Line 2096:	The document should detail that all relevant equipment used at the clinical site must be appropriately validated and maintained It is suggested the term 'Reconstitution' is replaced by 'Preparation' because this will be clearer and avoid confusion (e.g. it is debatable whether cell recovery after cryo-storage should be considered as a reconstitution). Whilst it is acknowledged these steps are often required for ATMP products because of their unique characteristics, these steps may constitute a considerable risk, requiring more specific guidance in this document. It could be specified that the combination of the ATMP with delivery systems, surgical devices, etc. should not result in a product meeting the definition of combined product.
17. Automated production of ATMPs	This section raises many complex regulatory and legislative issues and needs to be expanded dramatically to be of use to the community.