EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<01-Oct-2015>

Submission of comments on Consultation Document Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Art. 5 of Regulation 1394/2007

23/07/2015

Targeted stakeholder consultation on the development of Good Manufacturing Practice for Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation 1394/2007

- *Targeted stakeholders*
  All stakeholders involved in the development, manufacture and/or commercialisation of advanced therapy medicinal products. Comments from small and medium-sized enterprises (SMEs) are particularly welcome.
- *Period of consultation*
  From 23 July 2015 to 12 November 2015
- *Objective of the consultation*
  Article 5 of Regulation 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC requires the Commission to draw up guidelines on good manufacturing practice ("GMPs") specific to advanced therapy medicinal products ("ATMPs").
  With this public consultation, the Directorate General for Health and Food Safety intends to seek the view of stakeholders regarding the GMP requirements for ATMPs.
  The comments received will be taken into account by the European Commission when developing the Guidelines on good manufacturing practice specific to ATMPs.
- *How to submit your contribution*
  (Contributions should be sent before 12 November 2015 by e-mail exclusively to: SANTE-D5-ADVANCED-THERAPIES@ec.europa.eu) VIA the EUROPEAN QUALIFIED PERSON ASSOCIATION
  When you submit your response, please explain if you are acting as a private individual or on behalf of a company, association or other legal entity. Please state also your type of activity (e.g. R&D, manufacturing, marketing of ATMPs).
  If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50million annual turnover and fewer than 250 employees).
  If your organisation is registered in the Transparency Register, please indicate your Register ID number at the beginning of your contribution.
- *The consultation document*
  The consultation document can be downloaded here (190 KB).

Comments from:

Name of organisation or individual
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1. General comments

Stakeholder no. *<to be completed by the Agency>*	General comment (if any)	Outcome (if applicable) *<to be completed by the Agency>*
	Goal of this document Bio.be wishes to thank the European Commission for offering the opportunity for stakeholders to make comments. Adapted GMP for ATMP have drawn lot of attention since Regulation 1394/2007/EC, after some linked requirements in EudraLex Volume 4 of the "The rules governing medicinal products in the European Union" were found impractical, if not impossible, to comply with. Bio.be concurs with the Commission that a balanced and proportionate implementation of GMP requirements under EU Reg. 1394/2007/EC will allow new opportunities for the treatment of diseases and dysfunctions of the human body. However, it is of utmost importance to protect the health of patients from flexibility that reduces the standards of quality, safety or efficacy of medicine in the European Union. Therefore, this guideline should unambiguously identify where and how it supplements or supersedes, in whole or in parts, the 'regular' GMP requirements laid in EudraLex volume 4. It is offered for consideration to adopt an approach similar to that in Annex 14 of EudraLex v4 where specific requirements for manufacture of medicinal products derived from human blood or plasma are detailed. In	

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	doing so mutatis mutandis, attention should be drawn to terminology and a glossary be created to clarify the interpretation intended. Obsolete or newly-made redundant wording should also be removed from Annex 2 of EudraLex v4 (Manufacture of Biological active substances and Medicinal Products for Human Use), and harmonisation should be sought with existing guidance's in the field as well as with the (draft) document laying down requirements for raw materials for the production of cell-based and gene therapy medicinal products authored by the European Pharmacopeia. It should also be made clear where requirements apply to one, some or all ATMP subcategories (cell-based, gene vector based, engineered cells, combined…) Finally, aspects of ATMP manufacture and distribution that involve EU and non-EU environments should be detailed.	

2. *Specific comments on text*

Line No of the first line(s) affected <e.g. Line 20-23>	Stakeholder no. <to be completed by the Agency>	Comment and rationale; proposed changes <if changes to the wording are suggested, they should be highlighted using "track changes">	Outcome <to be completed by the Agency>
63-65		*§1. Introduction* *Additionally, early phases of research may take place in a hospital setting operating under a quality system different from the quality system typical of the pharmaceutical sector.* ***Comments:*** This wording is inappropriately recited from ICH Q10 as it allows clinical research to take place under any quality system, whether similar or not that typical in place in the pharmaceutical sector. Compliance with ICH Q10 (i.e. whatever the quality system, it offers comparable performance to that of the pharmaceutical sector) cannot be simply optional for early phases of clinical research. The quality system should be conceived and operated to protect the health of human subjects and to secure ethics and scientific interpretability of trial outcomes in and outside the EU.	
91		*"there is a quality control system which is independent from production"* ***Comments:*** This wording may not adapted to (very) small organizations that cannot be expected to show effective independence. ***Proposed change (if any):*** "there is a quality control system which is <u>operationally</u> independent from production"	

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102-127		*Chapter Risk-based approaches* ***Comments:*** This chapter discussing « risk-based approached » and "clinical vs. commercial" stage products is crucial for ATMP manufacturers. There are circumstances where a risk-based approach is desirable to substitute some "regular" GMP requirements. Though, this flexibility is limited and may not result in exposing subjects to clinically significant and improperly controlled risks, especially in early phases of clinical development. The clinical trial regulation EC/536/2014 provides that quality system in place could be commensurate to the clinical development phase. It is suggested to add direct reference to this wording in the Regulation to avoid misrepresentation in the guideline of the actual requirements.	
123-125		*In turn, the risk-based approach also implies that the manufacturer is responsible to put in place additional measures (beyond those suggested in the GMP Guidelines) if that is necessary to address the specific risks of the product.* ***Comments:*** It is unclear what "additional measures" mean under the risk-based approach scope.	

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Q1		*§ 2. GMPs for ATMPs: general principles* *Are the principles laid down in Section 2 (general principles) 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.* ***Comments:*** As stated in introductory comments, this document should be tailored to integrate into EudraLex v4. The simultaneous discussion of ATMP vs classical medicines and development vs. commercial stage is complex and should preferably be avoided as it is prone to misrepresentation of requirements set in EU legislation.	

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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.* ***Comments:*** Yes, certainly. The concept of risk-based approach is difficult to grasp, especially for clinical-stage ATMP. It is suggested that risk-based approaches are compiled, categorized (nature, stage of development), anonymized and made available for public consultation to provide generic hints about topics worth consideration and modes of resolution. Examples, depending on the clinical development stage: • Methods: introduction of QC tests on raw materials/consumables, on DS/DP • Validations: shipping, process reproducibility, process robustness, QC test methods. • GMP-level of compliance of subcontractors (materials and methods) should not be mandatory for phase I-II. • Limitation re: retention samples requirement in autologous setting. We also suggest having Section (2.1) about risk-based approach put in the context of 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) where the risk-based approach is a *strategy aiming at determining the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application* (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from the technical requirements as defined in Annex I, part IV of Directive 2001/83/EC. Thus the scope of the risk-based approach described in Section 2.1 is not clear, especially in the light of the following paragraph of the	

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Q3		*How should the quality systems established in accordance with Directive 2004/23 (setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells) 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?* ***Comments:*** FACT and JACIE are voluntary inspection and accreditation programs sponsored by the American and European Societies of Blood and Marrow Transplantation and the International Society of Cellular Therapy. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with these Standards does not guarantee compliance with all applicable laws and regulations. The FACT-JACIE introductory statement to quality reads "The major objective of the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration for Hematopoietic Cellular Therapies (the Standards) is to promote quality medical and laboratory practice in hematopoietic progenitor cell transplantation and other related therapies using hematopoietic-derived cellular products." (International standards for cellular therapy product collection, processing, and administration for hematopoietic cellular therapies, Draft 6th Ed, 2014). Thus it is also limited to a specific category of products (hematopoietic cells-related) and practice (medical and laboratory practice), and thus, it is not meant to address more than minimally manipulated cells. Thus, processing steps including rinsing, cleansing, sizing (non-exhaustive list) that allow to retain the structural function in an	

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103		*ATMPs are complex products and risks may differ according to the type of product.* ***Proposed change (if any):*** "ATMPs are complex products featured with specific risks."	
105-107		*It is also acknowledged that the finished product may entail a high degree of variability due to the use of biological materials and complex manipulation steps (e.g. cultivation of cells).* ***Proposed change (if any):*** *It is also acknowledged that the finished product may entail some acceptable degree of variability due to the use of biological materials and complex manipulation steps (e.g. cultivation of cells).*	

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110-113		*It follows that it is important to recognise some flexibility in the application of the GMP requirements so that the ATMP manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product.* ***Comments:*** The "flexibility" called for may be highly variable across EU MS inspectorates dealing with GMP certification prior to the conduct of clinical trials. ***Proposed change (if any):*** It follows that it is important to recognize departing from GMP requirements may be warranted having regards to the specifics of the manufacturing process and of the product.	

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Q4		*Are the requirements laid down in Section 3 (personnel) 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.* ***Comments:*** If the purpose of the document is to overrule EudraLex v4 chapt2, then the answer is negative. ***Proposed change (if any):*** All specifics of EudraLex v4 chapt2 should be declared as applicable, unless where directly overruled with adapted ATMP wording from this document.	
140-141		*Steps should be taken to ensure that health conditions of the personnel that may be relevant to the quality of the ATMP are declared.* ***Comments:*** This may not be properly worded. Sponsors/companies can only highlight specific risks to personnel and offer directions for appropriate protection of health status. They cannot require the health condition of an individual be declared.	

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144		*Health monitoring of staff should be proportional to the risks.* ***Comments:*** As stated above, at best a sponsors/companies can offer monitoring. It should be stated that it is the duty of the sponsors/companies to match the monitoring options offered with objective risks.	
144-146		*Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated.* ***Comments:*** As stated above, at best a sponsors/companies can offer vaccination.	
148-151		*In general, personnel should not pass directly from areas where there is exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled.* ***Comments:*** The wording proposed is prone to misinterpretation and reduction of the level of quality and safety because of the 'In general', 'should' and 'directly'. The cross-contamination prevention management (of biologics and/or chemicals) should be fit for purpose taking into account the specifics of the substances and processes involved and must always use effective and validated methods.	

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151		*If such passage is unavoidable, appropriate control measures should be applied.* ***Comments:*** The cross-contamination is likely not best described in personnel/circulation-dependent terms but rather in process dependent terms, for which numerous provisions exist in GMP that apply in ATMP settings. (E.g. line clearance, gowning, single-use equipment…). It is not acceptable to justify adapting (reducing from GMP expectation?) the level of quality (and thus safety) of ATMP on the ground that facilities are not really suitable for their manufacture.	
155-156		*Responsibility for production and for quality control cannot be assumed by the same person.* ***Comments:*** It is proposed to start the sentence with 'Operational responsibility' to better reflect situations in small organisation staff with operational responsibility also have global responsibilities. ***Proposed change (if any):*** Operational responsibility, because CEO is responsible for whole company.	

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179-181		*The manufacture of technical poisons, such as pesticides and herbicides, or cytotoxic agents, should not be allowed in premises used for the manufacture of ATMPs.* ***Comments:*** It desirable to make this statement more general. ***Proposed change (if any):*** Manufacture of ATMP should not be allowed in premises where handling of substances carrying a risk of metabolic toxicity to human or animal cells occurred, without prior effective decontamination.	
190-194		*Examples of such possible risk-mitigation measures include the use of closed systems, the use of self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning systems, campaign-based manufacturing, or implementation of adequate cleaning and decontamination procedures including the heating, ventilation and air condition systems.* ***Comments:*** It should be explicit that simultaneous manufacture of physically segregated batches is allowed (e.g. distinct cell cultures in closed vessels should be allowed in the same incubator)	

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202-203		*The laid out of the premises should permit the separation of flows of contaminated materials and equipment from those sterilized/non-contaminated.* **Comments:** Typo in text ***Proposed change (if any):*** The layout of the premises should permit the separation of flows of contaminated materials and equipment from those sterilized/non-contaminated.	
214-215		*For commercial production of ATMPs, the premises should be fully validated.* **Comments:** See also lines 711-713: *"they have to be qualified for clinical batches."* Could you please give some precisions? The requirement for GMP-validated premises for commercial medicines in already enacted. The issue arise from the clinical setting where the acceptable level of non-validation is not (yet) harmonized across EU MS. It is suggested to clarify that at minimum, the aerolic scheme, maintenance of adequate level of microbial and particular contamination, and critical equipment must be validated in the clinical development phase.	

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231-233		*Clean air devices should be classified in accordance with ISO 14644-1. In general, an A grade with a background of B grade is required for pivotal clinical trials and commercial production.* ***Comments:*** Environment control relates to contamination, and contamination to safety. So the control should be commensurate to the safety risk, not the clinical development phase. Closed-systems should be favoured. ***Proposed change (if any):*** In general, a grade A with a background of grade B, or a similarly controlled environment (note: to allow manufacturing plants in US, where definitions are slightly different), is required when an ATMP is not manufactured in a closed-system.	
246		*Clean areas should not have drains installed.* ***Comments:*** Ideally, drains should be avoided in clean rooms. In case of large scale allogeneic process, they might be necessary to dispose large volumes of culture effluents. ***Proposed change (if any):*** <u>Unless not avoidable given the manufacturing process,</u> clean areas should not have drains installed.	

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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?* ***Comments:*** We concur that the use of a clean room with an A grade with a background of C or D grade for early phases of clinical trials should be allowed. Such practices are already accepted elsewhere in the world (such as in the United States). Therefore the above mentioned proposal would increase alignment of the requirements between geographical areas and thus promote early clinical research in European institutions and enhance European company competitiveness Though, acceptability of this concept must be contingent to prior demonstration of robustness for safe manufacture with respect to contamination risks.	
248		*Production areas should be well lit, particularly where visual on-line controls are carried out.* ***Comments:*** No, some ingredients are light sensitive. ***Proposed change (if any):*** Lighting should be adapted to safe operations.	

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261		*Highly reactive materials or products should be stored in safe and secure areas.* ***Comments:*** 'Highly' is not defined. ***Proposed change (if any):*** Materials and product should be stored in safe and secure areas, per applicable legislation.	
271-272		*Premises where laboratory animals are kept should be well isolated from production, storage and quality control areas with separate entrance and air handling facilities.* ***Comments:*** 'well' is superfluous	
Q9		*Are the requirements laid down in Section 5 (equipment) 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.* ***Comments:*** Yes	

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277-279		*Manufacturing equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.* ***Proposed change (if any):*** Manufacturing equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive, adsorptive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.	
283-284		*Primary containment should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.* ***Comments:*** How should this sentence apply to single use primary containments? (obviously cannot be periodically tested) 'the immediate working' is superfluous.	

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291-294		*Automatic, mechanical or electronic equipment, including computers shall be routinely calibrated, inspected or checked to ensure proper performance. Written records of those checks shall be maintained.* ***Comments:*** It is suggested to rephrase and be more specific about expectations. What are the requirements regarding computer systems 'calibration'?	
294		*There should be sufficient controls to prevent unauthorised access to changes to data.* ***Proposed change (if any):*** There should be sufficient controls to prevent unauthorised alteration of original data.	
295-296		*Changes to data should be traceable (i.e. previous entry, date of change and identity of the person that introduced the change).* *Proposed change (if any):* Changes to data should be traceable with an audit trail (*i.e.* previous entry, date of change and identity of the person that introduced the change).	
311-312		*Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents throughout the retention period.* ***Comments:*** A minimal duration should be defined commensurate to the use of the data.	

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328-330		*Rationales for changes should be recorded and the consequences of a change on product quality and on any ongoing clinical trials should be investigated and documented.* ***Comments:*** Why only 'ongoing'? ***Proposed change (if any):*** Rationales for changes should be recorded and the consequences of a change on product quality on non-clinical and clinical trials and data should be investigated and documented.	
337-339		*Instructions for sampling and testing, as appropriate. For investigational ATMPs, the manufacturer may rely on the certificate of analysis of the supplier if this is considered appropriate having due regard to the risks.* ***Comments:*** Attention is drawn to the fact that reverse engineering of some raw/starting materials is not allowed. Their supply contract explicitly forbids testing the composition of matter that is not disclosed, with no alternative available. In such circumstance, the flexibility cannot be limited to the investigational setting and adapted means of control must (not should) be allowed to the ATMP manufacturer at any stage, clinical or commercial.	

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341 and 351		*Maximum period of storage.* ***Comments:*** The maximum period of storage may not be known or measurable (too small quantities). Therefore, where needed, scientific rationale should be allowed to substitute maximum storage specification, provided that consequential effect of outdated materials is controlled in the manufacturing process. The storage conditions should be added in list.	
342-343		*For raw materials of biological origin, the source, origin, traceability and suitability for the intended use should be described.* ***Comments:*** Some manufacturers will not provide this information, without recourse. Requirements for raw material specifications (line 342-343) should be more detailed and further clarified. We would recommend clarifying the difference between biological origin, source and origin. Alternatively, the text could refer to other regulations already in force. ***Proposed change (if any):*** Add '… to the extent possible' in sentence.	

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343-344		*For raw materials of biological origin […] contracts and quality requirements agreed with third party suppliers should be kept.* ***Comments:*** Contracts should not be an issue. Agreement on quality requirements may be/become an issue at any time in development. Suppliers of biological raw materials, may be/become without competitor, may argue these materials are for R&D purpose and thus, will not/no longer support their customers in this respect. It should also be mentioned that suppliers may be/become forbidden to provide the requested data or be/become genuinely unable to guarantee notification of change in the manufacturing process of raw materials. To make the situation even worse, it is sometimes forbidden to the ATMP manufacturer to test some aspects of quality of biological raw materials (testing being considered as reverse-engineering forbidden because of IP rights) A pragmatic approach should be that where it is showed not possible to obtain such information, a risk analysis should be accepted.	

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346		*Source, origin and suitability for the intended use should be described.* ***Proposed change (if any):*** Add '… to the extent possible' in sentence.	
365-367		*Release and rejection criteria for raw and starting materials, intermediates, bulk and finished product, including release strategy for characterisation results that are not available prior to product release.* ***Comments:*** It is not clear what it is meant in this sentence. It is our general understanding that characterization testing is usually not considered as part of the release and rejection criteria. Clarification would be useful. ***Proposed change (if any):*** Release and rejection criteria for raw and starting materials, intermediates, bulk and finished product, including release strategy for release tests results that are not available prior to product release.	

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382		*The contents will vary depending on the product and stage of development.* ***Comments:*** This sentence is obscure and prone to unacceptable practice. Protection of public health is the objective, records are the mean. The requirements for detailed records and their justifiable granularity for quality control throughout development stages apply irrespective of the ATMP nature of the product.	
397		*Batch number assigned after receipt* ***Comments:*** Do you mean the production batch in which it will be used? If positive then it is not always possible to foresee it. ***Proposed change (if any):*** To delete "Batch number assigned after receipt ". To add: "Shipping temperature and the storage temperature after receipt."	
417-419		*Note: Where a validated process is continuously monitored and controlled, manufacturing data might be limited to automatically generated compliance summaries and exception/out of specification data reports.* ***Proposed change (if any):*** Lines 417 to 419 are mentioned as "*Note*". We would recommend to fully integrate this point in the text.	

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423		*There should be appropriate documentation of policies and procedures to be applied by the manufacturer with a view to safeguard the quality of the product, including: Qualification or validation of processes, analytical methods, equipment and premises.* ***Comments:*** Please specify what should be expected in terms of validation/qualification per development stage.	
438-441		*For cell-based products, data ensuring the traceability of the finished product, it's starting and raw materials, including all substances coming into contact with the cells or tissues, should be kept for a minimum of 30 years after the expiry date of the product, unless a longer period is foreseen in the marketing authorisation.* ***Comments:*** For IMP, the batch documentation must be kept for at least 5 years after the completion/discontinuation of the last CT. (lines 428-431) whereas in lines 438-441, a duration of 30 years is mentioned. Is it for commercial cell therapy products only? In what format should this documentation be kept? ***Proposed change (if any):*** Harmonize to 30 years after the expiry date or use	

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455-458		*The donation, procurement and testing of human tissues and cells of used as starting materials or raw materials (e.g. feeder cells) should be in accordance with Directive 2004/23/EC. For materials that are outside the scope of the Directive, the ATMP manufacturer should take appropriate steps to ensure the quality, safety and traceability thereof.* ***Comments:*** Starting materials (donation, procurement and testing) for ATMPs can be regulated under Directive 2002/98/EC. This is mentioned lines 466-469 but could also be mentioned here and in the footnote related to line 512. It is important to note disharmony of interpretation across EU MS about cellular starting material under the scope of Dir 2004/23/EC and cellular blood-derived product under the scope of Dir 2002/98/EC. This should no longer be possible.	

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Q13		*Are the requirements laid down in Section 7 (SM & RM) 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.* ***Comments:*** Regarding the release testing of starting material used to manufacture autologous cell-therapies, we would like to emphasize that due to the limited amount of material available and also to the inherent inter-patient variability, it is sometimes impossible to develop methods able to inform about suitable quality of the starting material/raw material having regard to the intended use at release of the SM/RM. The release testing of bone marrow samples used for the manufacture of autologous bone marrow-derived mesenchymal stem cells is proposed here as an example. The fraction of MSCs found in the bone marrow (BMMSC) is estimated below 0.01% of total bone marrow cells. This amount is distributed in a complex matrix consisting of hematopoietic stem cells and a stromal fraction containing mainly fibroblasts, macrophages, osteocytes, chondrocytes and adipocytes. This forbids counting of the BMMSC using techniques based on flow cytometry (FACS). Density gradients methods such as Percoll and Ficoll-centrifugation require large volumes of bone marrow to be collected which is common practice in healthy bone marrow volunteers although not without risk, however, is not compliant with the patient population concerned which only allows non-invasive procedure for collection of relative small volumes of bone marrow. Therefore, initial isolation of BMMSCs only by their ability to adhere to plastic, to generate single-cell-derived colonies that can be expanded to obtain high numbers of cells, is standard practice and actually corresponds to starting the pharmaceutical product manufacturing process. It should be taken into account that some tests required for release	

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464-469		*The ATMP manufacturer should verify compliance of the supplier with the agreed specifications. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials. Blood establishments and tissue establishments authorised and supervised under Directive 2002/984 or Directive 2004/23 do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing.* ***Proposed change (if any):*** (464-465) *The ATMP manufacturer should verify compliance of the supplier's product with the agreed specifications.*	
486-488		*Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).* ***Proposed change (if any):*** (e.g. irradiation or filtration)	
490-491		*When antibiotics are used, they should be removed as soon as possible.* ***Comments:*** Removing of antibiotics may just be an insurmountable task. ***Proposed change (if any):*** When antibiotics are used, they should be stopped as soon as possible.	

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491-492		*Additionally, it is important to ensure that antibiotics do not interfere with the sterility testing, and that they are not present in the finished product.* ***Comments:*** They do interfere, that is their role. The point is that use of antibiotics cannot replace the requirement for a validated aseptic process. ***Proposed change (if any):*** Change "sterility" for "asepsy"	
507-509		*With a view to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers, starting materials should only be dispensed by designated persons.* ***Proposed change (if any):*** *Proposed change (if any):* *With a view to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers, starting materials should only be dispensed by trained persons.*	
513-514		*This means that the overall responsibility for the quality of the starting materials lies with the ATMP manufacturer.* ***Comments:*** This cannot be always achieved (confidential, refused by the supplier (with no alternate supplier), IP restricted...)	

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516-517		*As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under appropriate conditions.* ***Comments:*** This sentence appears obscure, what is the meaning?	

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522-524 and 749-752		*The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the marketing authorisation/clinical trial authorisation.* *In case of imports of investigational ATMPs from third countries, the QP must ensure that the quality of the batch is in accordance with the terms of the clinical trial authorisation and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EU.* ***Comments:*** Consideration should be given to not so rare situations where Out Of Specifications (OOS) of the IMP is not attributable to the manufacturing process but rather to idiopathic factors of the patient, and manufacture of a new batch is not an option. In such case, it may be preferable for the patient, in the interest of his/her health, to be dosed with an OOS IMP rather than not being dosed at all. It is suggested that where such situation occurs, guidance is available indicating that a) the treating physician is informed and his/her agreement to (not) use the OOS IMP recorded, and b) the competent authority + IEC are notified accordingly. Failure to manufacture, failure to release and failure to treat events could then be recorded without negative bias to the manufacturer or undue liability to QP.	

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548-550		*It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs* ***Comments:*** Splitting stocks at different locations may not always be feasible due to limiting, external factors. ***Proposed change (if any):*** Where feasible, it is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss.	
555-557		*In these cases, the lack of GMP compliance may require additional testing to ensure proper quality of the starting material.* ***Proposed change (if any):*** In case of lack of GMP compliance, risk analysis should be conducted to identify testing requirements needed to ensure quality of the starting material.	

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614-615		*The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.* ***Comments:*** This should be generalized to compatibility of labels (including leachables) irrespective of storage temperature. ***Proposed change (if any):*** The compatibility of labels with storage conditions (e.g. ultra-low temperature), should be verified.	
648-649		*For cell-based products, cleaning validation between the manufacturing of different batches should be performed.* ***Comments:*** We would suggest (i) to generalize to ATMP, (ii) to clarify this sentence, especially in the context of clinical trials (apply to any stage), and (iii) to consider risk based approaches as suitable means of compliance when manufacture campaign occur at distant moments in time.	

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652-653		*Centrifugation of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.* ***Comments:*** If the container centrifuged is closed (bag, tubes) and if the container's opening is done in contained area (e.g. biosafety cabinet in class A containing no other product), then there is no need to require centrifugation be done in a contained area.	
687-689		*Finished products should be held in quarantine until their final release under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation.* ***Comments:*** Release referred may not be 'final' e.g. intermediate release with asepsy testing data made available after use of product, only then allowing final release. Section 9.6 about finished product sounds inconsistent with Section 11.3.2 about batch release prior to obtaining the results of quality control tests. Clarification would be useful. ***Proposed change (if any):*** Finished products should be held in quarantine until <u>their release</u> under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation.	

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691-693		*Where additional donor (human or animal) health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.* ***Comments:*** Is it allowed to release DP if safety information on the starting material is incomplete or missing even in case of allogeneic products?	
695-696		*Starting and raw materials should either be returned to the suppliers or, where appropriate, destroyed.* ***Comments:*** There doesn't seem to be a GMP reason to specify what should be done further with such materials. ***Proposed change (if any):*** Starting and raw materials should be segregated from production environment.	

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705-707		*Returned products, which have left the control of the manufacturer, should be destroyed unless without doubt their quality is satisfactory after they have been critically assessed by the person/department responsible for quality control.* ***Comments:*** The sentence implies it would be reprocessed for clinical use only. That may not be the case as it could be used for quality/non-clinical R&D. ***Proposed change (if any):*** <u>Returned product (i.e. which have left control of the manufacturer) should be prevented from further clinical use.</u>	
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.* ***Comments:*** ATMP variability or batch size cannot justify escaping process validation requirements. Thus, a limit must exist to the level 'pragmatism', in the interest of patient health. Retrospective validation should be acceptable where time to manufacture, batch size, idiopathic factors (non-exhaustive list) make prospective validation unethical or technically over-demanding vs. the anticipated benefit for the patients	

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715-716		*Validation of aseptic processing should include a process simulation test using a culture medium (media fill test).* ***Comments:*** It is suggested ATMP manufacturer should comply with existing rules for aseptic process validation during all phases of clinical development except that frequency and extent of validation should be allowed to reflect the specifics of the ATMP manufacturing processes. This is to avoid holding the long-lasting steps (e.g. cell cultures for several weeks) because of interference with upcoming periodic (re)validation (usually twice a year). In addition, modularity of (re)validation should be allowed provided adjustment to the manufacturing process specific risks to avoid staff spending more time in (re)validation than manufacture.	

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722-724		*When any new manufacturing formula or manufacturing method is adopted, steps should be taken to demonstrate its suitability. Significant changes, which may affect the quality of the product or the reproducibility of the process, should be validated.* ***Comments:*** The wording about "validation of significant changes" deserve clarification. Validation of changes in a manufacturing process that is potentially not yet (completely) validated sounds confusing. Furthermore, additional requirements regarding comparability of the manufacturing processes would be useful. Given the inherent complexity of ATMP in clinical development focus should be more on control of changes and documentation thereof rather than continued validation.	
748		*The QP's main responsibility is to verify and certify that each batch produced in the EU has been manufactured and checked in accordance with:…relevant product specifications in the destination country (in the case of exports)* ***Proposed change (if any):*** (in case of exports or imports)	

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753-756		*In case of imports of commercial ATMPs from third countries, the QP must ensure that the quality of the batch is in accordance with the terms of the marketing authorisation, including by means of a full qualitative and quantitative analysis of the active substances as well as any other necessary checks, including re-testing.* ***Comments:*** 'full' is superfluous ***Proposed change (if any):*** In case of imports of commercial ATMPs from third countries, the QP must ensure that the quality of the batch is in accordance with the terms of the marketing authorisation, including by means of a qualitative and quantitative analysis of the active substances as well as any other necessary checks, including re-testing.	
758-760		*In such cases, the testing in the third country should be conducted under conditions equivalent to those applicable in the EU.* ***Comments:*** The term 'equivalent' is not defined. All methods applied in third countries that are approved for placement on the market in ICH countries should be presumed 'equivalent' without evidence. This would apply inter alia directly to serology testing kits not CE-marked but approved for the same intended purpose since, in practice, they cannot be repeated with CE-marked equivalent.	

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768-769		*QPs must have detailed knowledge of the product type and manufacturing steps for which they are taking responsibility.* ***Comments:*** We would recommend to have the wording "detailed knowledge" (line 768) clarified as in entails liability.	
811-812 and 951-953		*Checking that the manufacture and testing of the batch has been done in accordance with applicable requirements, including that:…all required in-process controls and checks have been made and appropriate* *records exists,* *In-process controls testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the product.* ***Comments:*** A specific issue with ATMP is that lack of quantities available in some batches may require that destructive IPC are skipped. This should be allowed and reflected in document.	
824-825		*It is acknowledged that not all of the elements above will be available in the case of investigational ATMPs.* ***Comments:*** Most of the items listed 11.3.1.(i) should be available for investigational ATMP: is it possible to list those that could not be available? (e.g. validation data on devices being adequate for the use in the combined ATMP)	

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832-835		*The register or equivalent document must remain at the disposal of the competent authority for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the QP, whichever is the longest.* ***Comments:*** Duration for retention should be harmonized, see comment above. (lines 438-441)	
836-840		*For investigational ATMPs, it is not necessary to create a register but the certification that the batch complies with relevant regulatory requirements must be made available by the sponsor at the request of the relevant competent authority. The certification must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.* ***Comments:*** A disharmonized interpretation of requirement exists across EU MS regarding the certification process: Should it be signed by the QP only, or by both the QP and the physician responsible for the tissue establishment that released the starting material? Could this point be clarified? Duration for retention should be harmonized, see comment above. (lines 438-441)	

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854-855		*The control reports or another proof of certification for release signed by the QP should be made available for the batches entering another Member State.* ***Comments:*** Could this be a certificate of release for shipping (without any CoA) if the batch is shipped under quarantine? Could one conclude that documentation requirements for release are higher when the ATMP is for non-domestic use? Is this compatible with EU rules regarding free circulation of goods and services on the one hand, and harmonization of standards for the protection of public health across EU MS on the other hand?	
870-872		*A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained after the release of the product.* ***Comments:*** This should be on top of GMP requirements for batch recall.	
883-885		*If a significant deviation in the manufacturing process described in the clinical trial dossier has occurred, the event should be notified to the relevant competent authority if the manufacturer wants to release the product.* ***Comments:*** See comments for lines 524-524	

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886		*Are the requirements laid down in Section 12 (QC) 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.* ***Comments:*** QC should relate to safety of the product rather than clinical stage, especially during early phases. LN2 storage should be discussed as whether, or not, requiring stability testing during the LN2 storage (the freezing/thawing should be tested, but what about the in-between when deep frozen? EU MS have different views on this.). The requirements laid in Section 12 do not fully address specific characteristics of autologous ATMPs, For example, stability monitoring programs for autologous products are particularly challenging because each batch produced is unique and often intended to be injected in entirety to the patient.	
900-901		*In-process controls may be carried out within the production area provided they do not carry any risk for the product.* ***Comments:*** This statement does not appear in alignment with lines 266-267, section 4.4: "Quality control laboratories should normally be separated from production areas."	

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922-925		*Samples are generally retained for analytical purposes should the need arise during the shelf life of the batch concerned (reference samples) and for identification purposes (retention samples of a fully packaged unit from a batch of finished product). Samples should be representative of the batch of materials or products from which they are taken.* ***Comments:*** It should be acknowledged that circumstances may be such that retention samples are not be identical to the DP (e.g. if not enough remaining cells). In such case, the Sponsor should evaluate representativeness in a risk-based analysis, and means of mitigation.	
936-937		*Containers should bear a label indicating, as a minimum, the content, batch number and date of sampling.* *Proposed change (if any):* Containers should bear a label indicating, as a minimum, the content, batch number and date of sampling, or an unambiguous reference to such records. (in case the container is too small)	

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938-945		*As a general principle, samples of starting materials (other than solvents, gases or water) used in the manufacturing process should be retained for two years after the release of the product. For investigational ATMPs, samples of starting materials should be kept for two years after the completion or formal discontinuation of the clinical trial in which the batch was used, whichever period is longer. However, in all cases, the retention period should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be acceptable. Samples of primary packaging material should be retained for the duration of the shelf-life of the finished product concerned.* ***Comments:*** To be aligned with lines 931-932, it should be mentioned that samples of biological starting materials is often not justified.	
957		*Testing methods should be qualified/validated (see Section 10) and reference materials should be established for qualification and routine testing if available.* ***Comments:*** This is apparent contradiction with what is mentioned in line 957, qualification/validation of testing methods are not clearly addressed in section 10 (only "control strategies should be under continuous supervision").	

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974-978		*The testing strategy may be affected by the limited availability or short-shelf life of certain materials. In such cases, consideration could be given to the following options:* *- Testing of intermediates or in-process controls if the relevance of the results from these tests to the intended material can be demonstrated.* *- Replacement of routine batch testing by process validation. While process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or not possible.* ***Comments:*** - Testing of intermediates or IPC: For which kind of material is it allowed? DP? - Process validation: This may not be realistic for autologous products	
1033-1034		*The contract acceptor should permit the inspections of the contract giver in connection with the subcontracted activities.* *Proposed change (if any):* The contract acceptor should permit the audits of the contract giver in connection with the subcontracted activities.	

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1058-1060		*An emergency plan dealing with accidental release of viable organisms should be in place. The plan should foresee measures/procedures for containment, protection of personnel, cleaning, and decontamination* ***Comments:*** Emergency plan dealing with accidental release of viable organisms for gene therapy could be part of RBA/RMP (to be reviewed during GMP inspections?)	

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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?* ***Comments:*** 'Validation of the reconstitution process' should be defined Considering the importance, 'validation' should always include demonstration of robustness (thus irrespective of development phase). Who is responsible of the reconstitution should be explicitly defined. The above definition of the "reconstitution" largely refers to EudraLex Vol 4 Annex XIII, Notes, 2nd note entitled "Manufacturing authorisation and reconstitution" which defines the inclusive list of manipulations of pharmaceuticals for which a manufacturing authorisation is NOT required. Any other manipulation does require a GMP-certified environment and a Qualified Person certification. " From the time of EudraLex Vol 4 release, ATMPs emerged and experience shows that, in a large number of clinical indications, (cryo-) preservation of cell-based products is desirable to overcome the short shelf-life of fresh cells. Thawing but also washing and centrifugation steps are necessary to remove the preservation solution (e.g. DMSO) and to reach adequate concentration for the finished product. Optimized removal of process-related impurities including residual amount of preservation solution is supposed to positively impacts the safety for the patient. However, the removal of preservation solution by successive washing and centrifugation steps goes beyond the examples of "reconstitution" proposed in the present Consultation Document which are limited to "*dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration*	

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Q23		*Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?* ***Comments:*** (See input to Q22 above) Post-processing activities when not affecting the therapeutic usability of an ATMP should be considered exempted from GMP and be considered a medical technique.	
Q24		*What activities should, in your view, be considered as reconstitution?* ***Comments:*** Reconstitution activities should consist in simple activities, with defined local operator intervention, performed in a validated system to demonstrate that (i) the closed system is a total containment device, or that it can be used in a non-sterile environment without contamination risk, (ii) quality criteria of the ATMP are maintained, (iii) process-related impurities are adequately removed or diluted. A large part of this debate stems from the use of the word 'reconstitution' which may not be best. Would 'preparation' be better?	

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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?* ***Comments:*** (see also comments to Q22-24 above*)* Automated devices where starting material is sampled and ATMP administered in the same procedure could be regulated under Dir 2004/23 as organ transplant for the procedure and as a device class III For the other cases, GMP should cover the technical functionality and capability of the automated equipment (manufacturer responsibility) whereas the process and the product obtained through the automate is under the responsibility of the site of use (hospital in general)	