EuropaBio comments to the DG SANTE consultation on GMPs for ATMPs

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 77 corporate and associate members and bio regions, and 16 national biotechnology associations in turn representing over 1800 biotech SMEs. EuropaBio's Healthcare Council represents both large biopharmaceutical companies and biotech SMEs developing medicines, vaccines and diagnostic tools using biotechnology in their development or manufacturing processes.

Transparency register number is: 1298286943-59

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Overall	EuropaBio welcomes this consultation and the Commission's desire to ensure that GMP requirements for ATMPs are proportionate and based on risk assessment. We would like to suggest the set up of an Industry-Commission meeting, perhaps also including the EMA GMP IWG, to discuss this document and its positioning with existing GMP requirements. Given the volume of comments, we would also like to ask for there to be a second consultation draft before this document is finalised. As a basis, the same principles as for EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines systematic (Chapters 1-9) should apply. In general the specifics around GMP requirements that are not changing when applied to ATMPs (like training requirements, Production area design, documentation….) should not be repeated. Instead the reference to existing regulations should be made and only points where either a different application is contemplated, or a relaxing of the requirement should be mentioned in this document. This will avoid redundancy and contradiction to existing requirements. We are concerned that those who are not engaged in mainstream pharmaceutical production may misinterpret the current level of detail in the document as the only requirements that need to be met. There is a need to either include or cross-reference significantly more of the text from Volume 4. Given that Hospital Exemption ATMPs are required to be of equivalent quality standard to those for which authorisation is required, and that the fundamental reason for GMP is to safeguard human patients/subjects, these guidelines should also apply to Hospital Exemption products. Within the introduction of the consultation document it is stated that the described GMP requirements should apply to manufacturers of ATMP for commercial distribution in accordance with the terms of a marketing authorization ("commercial ATMP"), as well as by manufacturers of ATMPs to be used in clinical Trials ("investigational ATMPs") (lines 69-72). The wording "commercial ATMP" in demarcation to "investigational ATMP" should not be used. It would be better to use the term "authorised ATMP" instead. The reason for that is that the term "commercial" is not a regulatory term and could – especially not always having the underlying definition in mind – lead to misunderstandings that those requirements are not valid for products that are not necessarily commercalised - e.g. in an non-industrial setting - although they need to be centrally authorised. That should be avoided. The scope of this guideline with regards to named patient/compassionate supplies should also be clarified Clear definitions of manufacturing operations versus reconstitution for ATMPs should be available to avoid national case-by-case assessments. Operations that fall under the definitions for reconstitution, should remain as broadly regulated as possible.

Introduction (intrinsic characteristics)	Intrinsic characteristics: should be added: - Not well characterized biologicals - Potential lifesaving benefit without failure tolerance
Priorities	The current version of the guide does not include provisions exempting from applying legal precautions for biosafety, environmental protection and work safety. The inclusion of some but not all biosafety or other legal rules is risky, as the reader may assume these rules are complete.
Definition	Definition of some terms should be in a dedicated definition section, e.g.: - Hospital - Large scale
Questions Q1	Pointing to a risk-based approach is helpful in enabling product and development phase appropriate flexibility whilst ensuring that specific risks are addressed. The text in Lines 120-122 should be clearly separated from that in Lines 118-120 to make it clear that any flexibility that may be warranted applies irrespective of manufacturer and is not limited to academic or hospital settings. Further, the "in particular for early phases of clinical trials" is not necessarily helpful, both because the term "early phases" is vague and because a risk-based approach may warrant flexibility irrespective of phase. Rather than use the term "acceptable level of quality", it might be beneficial to use the term "quality standard appropriate to the intended use", since this is the wording used in the definition of Good Manufacturing Practice (EudraLex, Volume 4, Part 1, 1.8) and therefore avoids the possible interpretation that this requirement is something different from GMP.
Q2	As per answer to Q1, we agree that a risk-based approach to the application of GMP to ATMPs is favourable. For example, meeting the requirements of sterility as per the EP (sample volumes, number of retains, etc.) is not always possible for gene modified cell therapy products because of limited starting material, the impact of donor variability manufacturing and clinical need. However, risk assessment/management is challenging to do well and more information than is given here will be needed to deliver the required outcome. It is suggested that this is not the place to provide this additional information. Instead, provide cross references to other guidelines where applicable. Separately, over time, consideration might be given to building a set of ATMP-specific case studies to further support organisations in this area. As example: replace entire Chapter 2 by: "Chapter 1 Pharmaceutical Quality System" applies. Exempt is

	- 1.8 (ix) GDP. The MAH defines the controls for the distribution. - 1.10 Product quality review. The MAH defines the structure and key indicators for the review. The risk management (1.13) should take in account the need for fail safe processes as potentially there is no chance for rework or repetition.
Q3	The question is unclear as to whether the EC is asking whether Directive 2004/23/EC be used alone or is the question whether the Directive be replaced by the JACIE accreditation system or that additional GMPs be established for the tissue collection practices. Directive 2004/23/EC does not appear appropriate to consider as GMPs. The Directive reads more as good "tissue" handling practices and does not speak to specific requirements that would support or ensure safety and efficacy of the product if the tissues are manipulated in any way. This Directive is not explicit enough as would be expected for GMPs during late-phase clinical or commercial manufacturing. The legal status of accreditation and the legal ability of JACIE to enforce its regulations and guidelines would need to be explicitly clarified in order to assess the adequacy of using accreditation to supplement GMP expectations. In addition, the expectation of the applicability of GMPs to starting materials should also be clarified. JACIE or equivalent could be recognized as the quality standard for cell procurement since it meets many of the underlying control principles of GMP. Since cell procurement results in starting material for an ATMP, and since the further manufacturing of the ATMP is covered by GMP, the question of GMP applicability to starting materials is important to resolve. IF the decision is that GMPs are not applicable for cellular starting materials, JACIE standards may be sufficient to assure starting material product quality, recognizing the need for flexibility of this approach. For commercial products, JACIE accreditation, in conjunction with sponsor qualification of procurement sites, can provide additional assurance that adequate controls are in place regarding the desired quality of the starting material, the traceability of the cells, training of personnel, adequacy of premises and documentation system etc. are met. Where possible, we recommend that the EC take into consideration the guidelines of tissue banks around the world to have consistent global standards for industry. This question should be answered together with responsibility for the biological starting material.
Q4	The requirements as laid down in section 3 seem to be standard and don't need to be restated. A reference to the existing requirements for GMP can be made here. The main area where section 3 could be further developed is the concept of cross-contamination (lines 147-151). In addition, as an ATMP may be in itself a GMO or contains a GMO, it might be worthwhile to refer to specific GMO guidelines or mentioning specific protective measures for GMO handling, when mentioning protective garments (lines 138-139).
Q5	Generally the requirements are appropriate with language allowing a risk-based approach in relevant places. Additional clarity would be useful to define where clinical manufacturing begins and where it ends. Accreditation standards or other controls may be of value at the collection site (prior to receipt at the manufacturing facility) and at the clinical site (after distribution from

	the manufacturing site). In line 231 there is a reference to ISO 14644, however there is no reference to Annex 1 EU GMP for microbiological limits and definition of grades. Apart from that the information in line 232 is vague as it implies early stage trials can be performed in a different environment. It is not always known upfront if a trial will be a pivotal study or not. In general there should be some reference to the potential use of isolator technology as this is an area of interest for the manufacture of ATMP's from both an aseptic and containment perspective. In line 234 a definition for large scale should be given
Q6	Although the 'in general' wording suggests that alternatives are possible, the sentence in Lines 231-233 requiring Grade A with Grade B background is restrictive and does not take account of current accepted practice where isolators are used (Grade C background is commonly used and Grade D background may be acceptable per EudraLex Volume 4, Annex 1, 23), nor does it allow for future technological advances – see comments on Question 8. It should not be assumed that higher standards must apply to commercial products. Particularly for autologous cell/gene therapies where there is no change in the scale of production with phase of development, premises for the manufacture of commercial products may well be the same as those used for investigational products. A universal definition of open and closed system would be useful.
Q7	Appropriate premises are fundamental to safeguarding patients/clinical trial subjects and whilst the scale may differ many requirements are independent of phase of clinical trial. Allowance of risk-based approaches adapted to the specifics of the product and manufacturing process, as currently within these guidelines, should enable appropriate action to be taken. In general, section 4 repeats a lot of the routine expectations of the GMPs and could be simplified through a cross reference. The document would be enhanced by providing guidance on expectations for control levels when manufacturing different cell products (allogeneic vs. autologous) and including some examples or points for the manufacturer to consider as they design and control their facility.
Q8	Use of a clean room with an A grade with a background of C or D would certainly enlarge the number of applicants potentially complying with this criterion. With adequate controls and risk mitigations (e.g., closed systems), it is feasible that background C or D might be appropriate not only for early phase clinical trials but for pivotal trials and commercial production too.. Consistently, it is not clear why GTMP (e.g. manufacture of ex vivo genetically modified cells) shall be excluded from the measure, considering that the primary aim of a suitable production environment is to minimize the risk of microbial contamination of the cells (regardless that these are genetically modified or not) during manufacture, and taking into account that vectors for GTMP production are currently manipulated in class B with a

	C background and can undergo final sterilization.
Q9	Section 5 does not seem to differ for ATMPs than for any other product types. The document might be simplified by cross-referencing to the already established GMP requirements.
Q10	Concerning line 316 the term "Product Information" could be misleading as it is widely used for the documents accompanying the product upon shipment. The statement in lines 337 to 339 is welcomed. In lines 417-419 the note is unclear. And in line 438 we have the question why the 30 year traceability requirement is only applicable to cell based products.
Q11	In general, the requirements appear to be appropriate. Traceability will remain an important concern for ATMP products thus documentation should underscore this.
Q12	All these requirements are equally applicable to investigational ATMPs as part of a robust quality system. The wording relating to retention of documents for investigational products based on the date of completion or formal discontinuation of a clinical trial is difficult to manage in practice. The manufacturer will want to comply with good documentation practice and archive records as soon as practicable after manufacture and to assign the retention period at this time. Therefore, retention periods are best based on the date of manufacture or date of certification. It is accepted that a longer retention period, e.g., 15 years, may need to be applied if the starting date is earlier. The requirement for a contract and quality agreement for each biological raw material in a less defined process is too stringent. This should at least be risk based.
Q13	Generally these requirements are appropriate; however some questions still remain open: for example in line 452 should this read ""5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS"" currently in draft. In lines 466 ff. the acceptance of licensed establishments without an audit requirement is fully endorsed. And in lines 481-484 we are not sure why this is specific to cell-based products. It should apply to any ATMP where sterilization is not possible. In addition, human tissues and cells used as starting materials or raw materials should be in accordance to tissues/cells directives but some disharmony is present at member state level (see for example Mycoplasma test mandatory for AIFA).
Q14	Since many ATMPs are cell products, this section on cell banks and seed lots would benefit from some further development. If the main focus of this section is for the generation of materials used in the production of ATMPs, that focus should be clarified, and a reference made to the content in ICH Q5D for creating, maintaining and documenting the derivation of these cell banks. Establishment and testing of

	seed lot and cell bank systems is an already well established procedure for production of rDNA molecules. It is not deemed that production of retroviral vector introduces critical differences in this step, therefore the already in use guideline with the proposed text provides a sufficiently well-defined frame for the applicant. If the section is aimed at ATMPs that come from seed lots or cell banks, then there are additional important criteria and controls established to manage and monitor tissue banks that should be referenced and expanded upon. The only room for flexibility would be in documenting the origin of the cell line which while critical, may be difficult for ATMPs (such as cord blood or other) given the need to respect patient privacy. It is recognized, however, that a non-well documented cell history might have safety implications. It should also be noted that in these cases, evidence of stability may occur concurrently for investigational ATMPs.
Q15	Generally the requirements are appropriate. Please see some specific suggestions below: In line 611 'preferably is a standard format throughout the facility' should be removed. There is evidence to show that changing the style and appearance of different labels can reduce errors. In line 618 the sentence ""Mix-ups of dedicated (autologous) materials should be prevented"" should be changed to materials for individual patients or equivalent. Mix ups of all materials should be prevented but just as important for an allogenic product for a specific patient. Not always autologous. In line 628 separations in place is somewhat vague. Allowance should be made where certain product stages require incubation of products in the same space. It may not be feasible to separate each lot of a given product, particularly for small scale individualised patient production. Some degree of risk assessment should be performed e.g. depending on whether the incubation is performed in an open or closed state. Add to the separation requirement ""unless completely closed processing is applied"". Line 648 requires cleaning validation. It is suggested that verification might be acceptable rather than validation, especially for early stages of development. In line 652 we do not believe this is true if closed vessels are used for centrifugation. Point 9.5 – Packaging materials: A step-wise approach in demonstrating compatibility of the primary packaging is advisable (and indeed already in force in practice), especially considering that most of the materials currently used for packaging ATMP products are already adopted for cell packaging in standard clinical use. It could be reasonable to include complete data package for compatibility for commercial applications and in case of large Phase III studies, whilst limited data can be required for first-in-man and Phase I/II studies.
Q16	We suggest that rather than the wording that "the manufacturing process for investigational ATMPs is not expected to be validated to the extent necessary for commercial ATMPs", which implies the manufacturing processes are expected to be validated to some extent, it is

	stated that "Manufacturing processes for investigational ATMPs are not required to be validated, but shall be appropriately monitored and controlled, taking into account the stage of product development, in order to assure the quality required for the intended use." - As per response to Q17, more detail regarding a pragmatic approach to process validation should be developed and included.
Q17	The principles of process validation can be applied using a risk based, pragmatic approach. Validating the process includes validation throughout the supply chain (raw materials, starting materials and the drug product itself, including methodologies). ATMP's pose several challenges, which will require control strategies based on a risk assessment approach. We recommend following the 3 stages of process validation prescribed in recent process validation guidance documents, with validation data coming from all 3 Stages rather than just emphasizing Stage 2 with a 3-batch rule. Allow for validation with representative cell type from healthy donors. Emphasize on-going data collection in the continued process validation stage and appropriate adjustments to control strategy based on the knowledge gained throughout product life cycle. Also for consideration, we would like to point out the possibility of an adaptive approach where the identification of surrogate markers reflecting critical quality attributes are continuously tested and assessed, either as part of the control strategy (analogous to PAT) or the release process, and serve as an alternative to process validation. This is akin to stringent continued process verification applied to each batch and provides a much more robust assessment of the state of control of the process given the high variability of the starting material. This does not preclude the qualification of individual steps or "unit operations" to perform their intended function.
Q18	There are a number of issues with the wording of this section. In particular: Wording in 841-846 is confusing and appears to be in contradiction to Regulation 536/2014. The two-stage release process in Lines 856-873 could also be significantly clarified. It needs to be clear that there is no need for competent authority approval prior to batch release in the event of an unplanned deviation if the points in Lines 875-882 are met
Q19	The section would benefit from the following improvements. In Line 895 there may be a need for some flexibility around the total independence of QC and production in the case of very small scale manufacturing for investigational ATMP's. QC activities must be performed by a trained individual independent of that specific production activity. In line 924 some guidance is needed for the manufacturing of individualised patient product where a single or very few units are produced. The retention and reference samples cannot always be fully representative in that for an individual patient product only one unit may be manufactured. In line 928 the retention of primary packaging and some expensive (non-biological) reagents ordered and made on demand is a huge burden and of very limited value and due to sampling constraints (one item only) rarely helpful in quality defect investigations. In line 938 it is not practical to retain samples of biological starting materials for individualised patient products. Lines 940-942: There should be no need for samples of starting materials for investigational medicinal products to be kept for a longer period of time based on the completion/discontinuation of the trial. The two years after the release of the product required for commercial products should be long enough. In line 957 in the same way process may not be fully validated for investigational ATMPs the same should apply to test methods. Those concerned with safety should be at all stages. Other tests may be performed for information only and may not be validated at this stage of

	product development. In line 985 it is stated that trending is not required for investigational ATMPs however this should be performed at all stages to determine what is important to product quality and what may not be. In line 1000 there should be guidance on stability expectations for investigational ATMPs.
Q20	The text is generally appropriate, but the scope should be any 'GMP activities' that are outsourced, not just 'manufacturing activities', and the proposed text confuses contracting and subcontracting – see specific comments.
Q21	Given the recent revision of EudraLex Volume 4, Chapter 8, to provide greater detail in response to issues identified by competent authorities, it is surprising that this section is so light. It seems to assume that 'complaint' and 'quality defect' are synonymous, which they are not – not all complaints relate to quality defects and not all quality defects are identified via complaints. There is no mention of the involvement of the qualified person, nor is there any tie with processes for dealing with suspected adverse (clinical) events.
Q22	Yes, the responsibility of the manufacturer should be limited to the development of the processes to be implemented at the infusion site upon receipt of the product, be it thawing and resuspension, or reconstitution, or dilution. The manufacturer should also specify "diluent" to be used, or provide it if required. The detailed information should be provided to the users.
Q23	Yes, in principle thawing and resuspension, or reconstitution are steps required for administration and are therefore covered by protocol instruction or for approved products, part of the Physician's instruction, and fall outside of GMP.
Q24	The guidance document that will be issued by the EC following this consultation should include a definition for "reconstitution" operation after batch release (that could include an exhaustive list of possible examples for reconstitution operation) but not just a list of examples. To answer the question, reconstitution could include thawing steps, but not buffer exchange, gentle agitation of the container to distribute cells evenly, drawing up of a cell suspension into a syringe, or adding a cell concentrate to an infusion bag containing an infusion solution. It might also include split of product in several applications and reconstitution and use on several days. Any and all of these options should be fully supported by development activities at the manufacturer and be described in the label.
Q25	There is certainly a lot of interest in these concepts and in the advantages they could offer, especially if the systems are closed as then (as also mentioned in previous responses to Question 8) the background air cleanliness requirements may be relaxed subject to justification. Automated systems implemented to culture ATMPs outside of a traditional manufacturing location should probably be considered as medical devices. Quality is one of the responsibilities of the user. GMP may not apply however the organization should have a quality system (e.g. following and being certified for ISO 9001).. The broader legislative implications of use of such automated systems to manufacture an ATMP "at the bedside" requires additional discussion. For example, is product processed by such devices 'manufactured' and, if so, what are the implications for facility licensing, GMP and QP certification? What are the responsibilities for assessing any adverse events and where does liability sit in the event of a

	significant failure? We would be keen to progress such discussion in parallel with work to address the technical challenges. Whether such devices are used in a traditional manufacturing setting or in a hospital setting, the devices should be installed by qualified personnel from the supplier incl. IQ/OQ documentation where possible. A periodic service and/or calibration should be performed which, alongside in process controls and strict quality specifications, should ensure correct performance of the device. The process must be thoroughly assessed for risks especially remaining open procedures that could affect the closed system status - the linchpin of the whole concept - must be addressed carefully (eg. due to IPC/QC sampling, preparation of buffer/media, buffer/media exchange during processing, final formulation etc.). A sophisticated barcode-label-documentation system or equivalent to prevent mix up of materials (starting and raw materials, excipients, final product) including IPC-, QC- and backup-sample handling is also required. National blood banks could be a reference for this. Particular attention has to be taken for automated systems including software that has been designed specifically for the individual user. Clearly defining responsibilities would be challenging and for the avoidance of doubt should be subject to written contract between all concerned parties. For EU member states the Qualified Person who certifies and releases the batch is one important responsibility partner. Other important players are manufacturing, marketing authorisation holders, sponsors of clinical trials and of course the tool providers themselves who are enabling closed automated production.

Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes
73/74	Comment: Why exempt the manufacture of ATMPs under Hospital Exemption from the scope of GMP? Whenever a product is produced for human administration GMP should be applicable. Suggest: Remove the exclusion of Hospital Exemption manufacture from the scope.
81	Comment (Low Priority): There is no mention of the control of outsourced activities within this listing Proposed change: Add in that "Any outsourced activities are governed by a written contract which clearly establishes the scope of work, required standards and responsibilities of each party.
94-96	Comment: Self-inspections are expected per lines 94-96 in Section 2, but there are no further details provided. Proposed change: Add in a section on self inspections based on EudraLex Volume 4, Chapter 9
115-122	Comment: While the point is clear that flexibility is warranted for early phases of clinical studies, it would be helpful to be clearer with respect to what flexibility would be allowed. Even if the ATMP manufacture is performed in an academic or hospital setting, basic controls on the environment and on personnel qualification and performance are expected. Proposed change (if any): Suggest that the flexibility be tied to product knowledge and re-emphasize that product "safety" from a microbial content or an adventitious agent standpoint should still be ensured. Perhaps also restate that facility cleanliness concepts, personnel training, and equipment calibration would still be required.
115-122	If the previous recommendation to replace this section with a reference to Chapter 1 is not adopted, the recommendation is to take out lines 115-122 and replace by (out of chapter 1):

Line number(s) of the relevant text	Comment and rationale; proposed changes
	<u>Quality Risk Management</u> Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively. The principles of quality risk management are that: i. The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient ii. The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk. Examples of the processes and applications of quality risk management can be found inter alia in ICH Q9 which is reproduced in Part III of the Guide. The risk management (1.13) should account the need for fail safe processes as potentially there is no chance for rework or repetition.
128-156	Replace by: - Chapter 2: Personnel applies. - Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use, Chapter Personnel applies; the monitoring of the staff should be adapted to the viral platforms used.
132	Comment (Low Priority): "understanding of its tasks..." Proposed change: "understanding of **their** tasks..."
144-147	Comment: This section states, "Health monitoring of staff should be proportional to the risks. Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated." While we appreciate the qualifying phrase "proportional to risk" again recognizing the application of flexible standards, the statement is quite broad and perhaps specific guidance should be provided as to what pathogens personnel should be vaccinated against.
147-151	This section could be further developed with examples focused on the differences in expectation or acceptability (if any) for production of allogeneic cell therapies or autologous with respect to risk of cross-contamination due to personnel. This same comment is valid for lines

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	162-166 in the following section, but with respect to facility design and facility flows.
152-156	Important is the independence, not the appointment. This text could usefully be expanded to make clear the requirement for job descriptions and to ensure that there are no gaps in responsibilities
157-272	Replace by: - Chapter 3: Premises applies. 3.6 Dedicated facilities should be changed in that the viability and pathogenicity of organism should be evaluated for decisions. Biosafety rules always apply. For the operation and maintenance of clean room installations Annex 1: Manufacture of Sterile Medicinal Products should be applied.
168	Comment (Low Priority): Include the requirement for cleaning to be covered by written procedure. Proposed change: "Premises should be kept clean by cleaning and, where applicable, disinfecting according to detailed written procedures."
185-187	Biosafety should apply and be mentioned at the very beginning of the guideline.
202	Typo, should read "layout" not "laidout"
208/230-233	Guidance is given for open processing (A/B). However, no guidance is given for fully closed processing. For example if the use of fully closed processing is used, or if "open steps" are performed in an isolator, it should be acceptable to locate these processes in such cases in a Grade C or D environment so long as the control of material and personnel flows and cleanliness are maintained.
210/211	Comment (Low Priority): Suggest delete the sentence "Special attention should be paid to products for which there is no sterilisation of the finished product" because this will be the routine situation for ATMPs and the converse situation is covered by the sentence in Lines 212-214 Proposed change: Delete the sentence "Special attention should be paid to products for which there is no sterilisation of the finished product"

Line number(s) of the relevant text	Comment and rationale; proposed changes
212-214	Comment: Perhaps the author meant to write the following: Propose change: "The measures implemented to ensure an aseptic environment should be adequate having regard to all the specific risks of the product. If sterilisation of the finished product is not possible, particular attention should be paid to the filling process."
214-215	Comment: Facilities and equipment are 'qualified' rather than 'validated' Further, the term "fully validated" is used, but the meaning of this is not given. It is suggested that cross-reference is included to Volume 4, Part 1, Annex 15. Proposed change: "For commercial production of ATMPs, the premises should be fully qualified in accordance with EudraLex Volume 4, Part 1, Annex 15."
231	Comment: The proposed wording is not consistent with current manufacturing for injectables when carried out within an isolator (Grade C background frequently used and EudraLex Volume 4, Annex 1, 23, allows for the possibility of isolators to be operated in a Grade D environment). Proposed change: That statement should be qualified to state unless carried out in a closed system…
232	Comment: Please see comment to line 231 above. With adequate controls and risk mitigations (e.g., use of closed systems) this should be acceptable not just for early phase trials but also for commercial manufacturing. Future ATMPs will need some innovative manufacturing solutions which may not fit current sterile manufacturing paradigms. The requirements should therefore be flexible with a focus on detailed evaluation of risk and mitigation of that risk to provide the required sterility assurance. Proposed change: "In general, an A grade with a background of B grade is required for pivotal clinical trials and commercial production" to: "Air classifications should be determined and justified through risk assessment to assure product sterility taking into account the nature of

Line number(s) of the relevant text	Comment and rationale; proposed changes
	the product and its processing, including consideration of operational enclosure."
240/ 240-246	What constitutes "Large scale?" Propose to delete lines 240 to 245. Keep only 246
244	Suggest "Developers" should be "Manufacturers" Proposed change: "Manufacturers are reminded that..."
246	Comment (Low Priority): "Clean areas ..." The use of 'Classified Grade A/B areas' would avoid risk of confusion from use of word 'clean', since all premises should be kept clean (168) and drains may be appropriate in places. "Classified Grade A/B areas should not have drains installed."
261	Comment (Low Priority): Draft text here has "Highly **re**active" vs "Highly active" of Volume 4, Part 1, 3.24. Perhaps both should be covered? Proposed change: "Highly active or reactive materials and products should be assessed to ensure their appropriate safe and secure storage."
266/267	Comment (Low Priority): Reference is made to further details about quality control laboratories in Section 12.1, but this section does not include further details about testing facilities. Proposed change: Incorporate here (and remove reference to Section 12.1) or within Section 12.1 (retaining existing wording here) the further details required.
280-282	Cleaning needs to be carried out in accordance with a written procedure and there should also be controls over cleaned equipment. It needs to be ensured that cleaning equipment is not a source of contamination.

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Add extra text drawing from Volume 4, Part 1, 3.36/3.37. E.g., "The equipment must be cleaned and stored appropriately in accordance with written procedure in order not to be a source of contamination. Washing and cleaning equipment should be chosen and used in ways that ensure they do not become a source of contamination. Single-use, disposable, equipment parts should be used where posible. Sterilisation of multi-use…"
283-284	Delete, repetition (274), biosafety e.g. 187; all biosafety rules apply as discussed in introduction.
288-293	Comment: 291-293 essentially repeats 288-290. Proposed change: Delete 291-293
294	Comment (Low Priority): This sentence does not read quite right Proposed change: Suggest: "There should be sufficient controls to prevent unauthorised access to data which would enable changes to be made."
294-296	Given all the current concerns about data integrity, this section is far too light. Reference to, or text from, Volume 4, Part 1, Annex 11, should be included here. In particular, there should be text included regarding the importance of data audit trails.
Section 6	There is reference to SOPs in Line 306 and to procedures being applied to qualification/validation and investigations in Section 6.4. There are, however, no stated requirements for procedures to be used to ensure this documentation is delivered.
301	Proposed change (Low Priority): "... and is **a** key element of ..."
313	Comment (Low Priority): Why should only commercial manufacturing sites require site master files? The creation of a site master file is a useful exercise to ensuring that key quality systems are in place and is therefore of benefit for any facility producing products intended for human use. Proposed change: Delete 'commercial': "A site master file should be prepared for every site involved in manufacturing."
323/324	Comment (Low Priority): Does not read quite right.

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Proposed change: Suggest "... **complies with the relevant quality specifications**."
330-333(and other sections, eg. 727)	It is clear that changes which have an impact to the process or the product need thorough evaluation and may require competent authority agreement, but if the document could provide more substantive description or some examples of "substantial modifications" for investigational ATMPs it would be helpful. Alternatively, if the decision is to keep the guidance on general GMPs in this document, and since change control belongs to the "Quality System" wording of chapter 1, we recommend that these lines could be deleted.
336-344	If the raw materials (such as cytokines, or other biological materials) are covered by an approved Market Authorization, it should be acceptable to rely on the Certificate of Analysis for the material and not be a requirement to repeat the testing.
336-353	Raw and starting materials: is split in too many chapters see as well 442-514, 585-615 Raw and starting material should be defined (see above). Add in: "Instructions for sampling and testing, as appropriate." Proposed change: Suggest: "For investigational ATMPs, the manufacturer may rely on the certificate of analysis of the supplier **if justified in a documented risk assessment. Consideration should still be given to minimum testing to assure quality.**"
341	Comment: Suggest that storage conditions should also be specified. Suggest: "Storage conditions and maximum period of storage"
365-367	The Manufacturer (of the ATMP) should issue a Certificate of Analysis. This may be required for the processing/compounding for use of the product (e.g. number of cells).
368-372	We are of the opinion is that this section is not applicable for ATMPs as in most cases, the "packaging" is for a single patient. The focus should be modified to address traceability through the entire supply chain and not on "reconciliation" of a small number of packaged units.

Line number(s) of the relevant text	Comment and rationale; proposed changes
375-376	Instructions for product preparation prior to administration should be developed in detail and provided by the manufacturer for the clinical setting, and is expected to be part of the label for approved medicinal products.
377	Comment (Low Priority): Should be 6.4, not 6.2.2 Proposed change: Correct and address knock-on impact on Lines 420 and 426
378-379	Comment: The sentence contains the following phrase, "any significant deviations should be recorded and investigated" Inclusion of "significant" could prove to be problematic since it then leaves it open to judgement what level of deviation constitutes a significant deviation. Would suggest consideration be given to remove "significant" from the sentence Proposed change (if any): Any ~~significant~~ deviation~~s~~ should be recorded and investigated, and appropriate corrective measures should be taken.
382-386	Requirements of Annex 13 should be referenced. While it may be acceptable for records limited to information of relevance to activities in respective locations to be under the oversight of "local" QPs, the comprehensive review of the manufacturing steps in their entirety against the product specification should be ensured. This may be difficult given the non-centralized clinical trial application system in the EU.
385	Proposed change: Change 'files' to 'records'
394	*Supplier's* batch or…
411	Better wording than 'special problems'?
417-419	We understand that provisions exist for the use of electronic Batch recording and do not think these lines provide any benefit to the document.
420-425	This 'other documentation' list appears to be very short and, although it uses the word 'including', does not point to other elements. Proposed change: Consider inclusion of other elements in EudraLex 4.29 – 4.31 here.

Line number(s) of the relevant text	Comment and rationale; proposed changes
427-440	Clarity with the requirements from Annex 2 should be assured. Annex 2 requires batch documentation also be kept for 30 years. Good documentation practice will archive records as soon as practical after their creation and assign the retention period at the time of archive. Therefore, it is preferable to set the retention period based on a date that is already known, e.g., date of manufacture, rather than on a future date, such as 'completion or formal discontinuation of the last clinical trial in which the batch is used' However, a thirty year record retention requirement for any material coming into contact with cells may prove to be quite burdensome to sponsors. Additionally, the expectation that records be kept for a minimum of 30 years after product expiry is very lengthy. We encourage some flexibility in the amount of documentation kept per batch. For example, retaining only final product records (as long as all materials can be traced back to their source) rather than retaining all incoming and processing records for the entire retention period. Suggest: "For investigational medicinal products, the batch documentation must be kept for at least 15 years after the date of manufacture."
450-45	We recommend that the general chapter of Ph. EUR remains referenced in this document and that the further detail not be repeated. Additionally, we recommend that the definitions of Raw Materials and Starting Materials be clarified and aligned with the general chapter.
455	Typo: 'and cells ~~of~~ used as starting materials'
464	Propose that the sentence be modified to address compliance of the *supplier's materials* with the specifications.
467-469	Citation of the directives should be consistent e.g. Directive 2004/23/EC[2] and pointing to same footnote. "Do not require…".This is valid as well for autologous graft. These are excluded in Directive 2004/23/EC[2] however, it is extremely important that not each hospital or even surgical team needs to be audited by the manufacturer. Organizations showing compliance with Directive 2004/23/EC[2] do have the necessary quality system and can use it for autologous graft.
485	Prior to stating that where possible, sterilization of starting materials and raw materials should be performed by heat, it is important to stress that the sterilization process should be shown to be effective both in removing or reducing the contaminants and preserving the

Line number(s) of the relevant text	Comment and rationale; proposed changes
	activity of the material (particularly for raw materials and excipients). As in other parts of the document, the guidance should be based on applying knowledge of the material and appropriate evaluation for risk. All of the techniques can be considered as effective when appropriately applied and verified, and therefore, one should not be emphasized over another.
485-488	Where possible the choice of sterilization method follows the decision tree. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003520.pdf
489-492	Use of antibiotics: if Penicillin type antibiotics are used no other products should be produced on same line? Use and type of antibiotic should be listed on product label?
493-499	Suggest that labels should also include storage conditions to help ensure that materials are kept appropriately. Proposed Change: Add to this list '- storage conditions'
500	Automated system should be allowed. Use of barcode on raw material container, bulk containers and samples would be more important.
501-506	The use of starting materials that have not been released should be exceptional and there should not be occasions when products are released before the quality of the input materials have been assured. There is reference to section 11.3.2 here, but that section only covers the situation where it has not been possible to complete all quality control tests on the product. Proposed change: Two options suggested: (1) Delete this whole section so as not to create the suggestion that use of starting materials before their full approval is part of good manufacturing practice OR (2) Truncate the last sentence and delete the "unless appropriate risk mitigation measures are possible" text to leave: "In such cases, the finished product can only be released if the results of these tests are satisfactory."

Line number(s) of the relevant text	Comment and rationale; proposed changes
507 – 510	This section appears to be repetitive. We recommend removing these lines.
511-512	Trace out, has been ruled in this guidance.
513-514	Misleading. For starting materials following 2004/23/EC[2] the ATMP manufacturer cannot take over the responsibilities. For all others, standard GMP is applicable. See as well annex 2. Trace out.
516-558	Annex 2 "Manufacture of Biological active substances and Medicinal Products for Human Use" does include Gene therapy: genetically modified cells, Somatic cell therapy, Tissue engineered Products. There is no need for duplication. Trace out except the last paragraph: Deviations may be scientifically justified and used as approved in the Marketing Authorization or Trial protocol.
538	The use of the term "Cell-based products" is a bit confusing as the text is likely not referring to an allogeneic or autologous cell product. But this is unclear. If the text is referring to these cell products, it would be beneficial to clarify this. Then also many more requirements apply to the cell stock than those listed here.
554-558	Comment: This paragraph would benefit by providing a few examples of what would constitute "exceptional and justified cases" where cell stocks/cell banks and viral seed stock may be accepted without full GMP compliance.
571	Proposed change: "Changes to the manufacturing requirements..."
573	Proposed change: "and substantial modifications..."
595-727	No need for this chapter. Follow the cGMP, however, if it is not removed, please see additional comments below:
644/645	Comment: 'concurrent manufacture in the same area' It need to be clarified what is meant by 'area'. For example, if vectors are processed within isolators, is it the isolator that is the 'area', or the room in which the isolator is situated? If the former, then more than one isolator could be in a room and it would be possible to process vectors at the same time, subject to appropriate assessment and mitigation of any associated risks. If the latter, then only one

Line number(s) of the relevant text	Comment and rationale; proposed changes
	isolator could be used at any given time. Clarify: Propose that an isolator could be defined as an 'area'.
648	Comment: Does there have to be cleaning validation, or might verification be acceptable? Proposed change: Change 'validation' to 'verification'?
687-689	As acknowledged in other parts of this document, many cellular therapies must be released before final test results are available. Sufficient flexibility should be allowed such that quarantine requirements do not conflict with expedited release strategies. However, that is not clear in the way the document is currently written.
716	Replace the term "media fill" with "aseptic process validation" to distinguish from stand Fill/Finish processing of steriles.
728-999	We believe that the focus for these sections can be reduced to those sections that provide additional guidance relevant to ATMPs, and that beyond those called out sections, a reference to the GMP requirements already codified is sufficient. For example: - 11.3.2. Batch release prior to obtaining the results: (lines 865-869) - Sampling of starting materials: (930-932)
753-774 768	The document provides good recommendations for how an ATMP from a third country is handled in the EU with respect to QP oversight and release. Similar to the comment in 382-386, consideration should be given to how the information is consolidated and available to the QPs for a comprehensive review. In addition, guidance for how investigational ATMPs from a third country would be handled in the absence of a centralized system for clinical trial application approval would be helpful. Specifically within the section: Proposed change: QPs should have detailed knowledge..."

Line number(s) of the relevant text	Comment and rationale; proposed changes
836-838	Comment: The requirements for 'a register or equivalent document' are loose enough not to need to exempt investigational ATMPs from these requirements given that the certifications must be made available anyway. This wording also contradicts the proposed wording of the Delegated Act on GMP for IMPs which does require 'a register or equivalent document'. Proposed change: Delete this sentence
838-840	Comment: A retention period based on the completion or formal discontinuation of the last clinical trial in which the batch is used is difficult to manage. Good documentation practice is for documents to be archived as quickly as possible and for the retention period to be set at time of archive. A fixed period, as for commercial ATMPs, would be better. To allow for the additional time associated with trial completion, a period of ten years from date of certification is suggested. Proposed change: "For investigational ATMPs, the register or equivalent certification documentation must be kept for at least ten years after certification of the batch by the QP."
841-846	Comment: This paragraph is confusing with regards to definition of manufacture/manufacturing authorisations. If packaging and labelling is carried out at a sponsor site, then it should clearly be an authorised site and require a QP certification. There is no exemption for sponsor sites in Reg 536/2014, Article 61(5)(a). Any exemption for hospitals, health centres and clinics needs clearer definition.
856-873	Comment: This section appears to relate to the two-stage release process that may be applicable to short shelf life products which require

Line number(s) of the relevant text	Comment and rationale; proposed changes
	administration before it is possible to complete full analytical testing, but would benefit from greater clarity. Should include minimum tests to be completed for stage 1 release Proposed change: "**Where specified in the marketing authorisation or clinical trial authorisation, ATMPs with short shelf lives requiring administration before it is possible to complete all quality control tests, may be subject to a two-stage certification and release process:** - Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures, and the available analytical results for review in preparation for the initial certification by the QP**, which allows release for administration**. - Assessment of the final analytical tests and other information available for final certification by the QP. **A procedure should be in place detailing the whole release process, including** responsibilities of the involved personnel and the continuous assessment of **batch data between the initial and final certification. The procedure should include description of** the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained after the **initial QP certification and release for administration, thus preventing final certification.** Such events should be fully investigated..." Add in: "Minimum testing required for Stage 1 release/certification must be defined in site processes/procedures".
871	Comment (Low Priority): "…where out of specification test results…" Proposed change: Change to "…where **confirmed** out of specification test results…"
875	Comment: Delete 'active substances' and 'excipients' from this text as these are not materials produced under the scope of this document and subject to QP certification.

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Proposed change: "As long as the product specifications are met..."
883-885	Comment: This should be reworded to make it clear that the requirement is a notification only and that no response is required from the competent authority before product release. It is also suggested that this is equally applicable to commercial ATMPs. Proposed change: "Information on batches certified following such an unplanned deviation should be notified to the relevant competent authority"
865-869	Copy the annex 3: Some ATMPs may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed. ATMPs product release may be carried out in two or more stages, before and after full analytical testing: a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the ATMPs under quarantine status to the clinical department. b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Qualified Person. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained. - Most ATMPs are intended for use within a short time and the period of validity with regard to the biologic shelf-life, must be clearly stated. - ATMPs having long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the QP. - For each ATMP, feedback from the clinical staff on the biological characteristics should be received to ensure the stability of the process.
903	Comment (Low priority): Minor wording change proposal since a person is being referred to

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Proposed change: Change 'it assumes' to 'they assume'
924	Comment: The requirement to retain a fully packaged unit of the finished product cannot be achieved for some autologous products, where the entire batch may be a single unit. Suggest: Alternative ways of meeting the need for identification, e.g., label copy in batch records, photographs, should be allowable.
928	Comment (Low Priority): Minor typo – it is samples that are kept, not sampling. Proposed change: 'Sampling' should be 'Samples'
935	Comment (Low Priority): The use of 'etc.' is not helpful guidance as it leaves too much open to interpretation. Proposed change: Use the list in current EudraLex Volume 4, 6.11 here
936	Comment (Low Priority): It should be clarified that the containers being referred to here are the sample containers Proposed change: "**Sample** containers should bear..."
940-942	Comment: There is no justification for samples of starting materials for IMP ATMPs being kept for a longer period of time based on the completion/discontinuation of the trial. The two years after the release of the product required of lines 938/939 should be long enough in all cases. Proposed change: Delete the sentence "For investigational ATMPs..."
944	Comment (Low Priority): Retention for duration of shelf-life of the product only? Would have expected this to be at least a year after the expiry date of the finished product. Proposed change: Suggest "...retained for one year past the expiry date of the finished product concerned."
943	Comment: It is not clear whether the shorter periods that 'may be acceptable' are down to manufacturer justification or whether these

Line number(s) of the relevant text	Comment and rationale; proposed changes
	need to be included in CTA/MA or otherwise agreed with regulators. Proposed change: Suggest change to "...therefore, shorter periods may be applied when supported by a written justification by the manufacturer."
946-949	Comment: Whilst the flexibility is of some benefit, from a guidance perspective some additional text here around the considerations of sample storage under label storage conditions or conditions that maximise stability might be beneficial. This is especially the case for short shelf life products. Proposed change: "Reference samples should usually be kept at the label storage conditions so that they are fully representative of the product that has been supplied. For products with short shelf life, however, samples at label storage conditions will rapidly cease to serve any useful purpose and in such circumstances the use of alternative storage conditions that maximise stability should be carefully considered and the decision documented."
1001-1007	In cases of short shelf life or limited available material, the feedback for biological characteristics from the clinical team for each single ATMP should be careful analysed and trended.
1008-1034	This should again exclude the organizations showing compliance with Directive 2004/23/EC2 or Directive 2002/98/EC4. This should include the (micro-) biological laboratories at those sites as certain tests on pathogenic organisms will be extremely difficult to outsource elsewhere. Specifically in this section, see comments below: Line 1010, suggest: "~~**Manufacturing**~~ **Any GMP** activities that are outsourced..." Lines 1014 – 1017:

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Comment (Low Priority): If outsourcing, the contract giver may not be 'the manufacturer' and the contract acceptor may not be a subcontractor – they may be the primary contractor. Proposed change: Suggest: "Prior to outsourcing any activity, the ~~**manufacturer (**~~"contract giver"~~**)**~~ should assess the suitability of the ~~**subcontractor (**~~"contract acceptor"~~**)**~~ to carry out the ~~**sub**~~contracted activities..." Lines 1018/ 1019: Comment (Low Priority): This text may not be appropriate, depending on the activities contracted. Proposed change: Suggest: "The contract giver should provide the contract acceptor with the detailed information necessary to carry out the contracted operations correctly." Lines 1020/ 1021: Comment (Low Priority): This is guideline, so 'must' should be changed to 'should'. The inclusion of 'analytical results' creates a greater level of specificity than in necessary. Proposed change: Suggest: "The contract giver **should** review and assess the records and **any results** related to the outsourced activities." Line 1033: Comment (Low Priority): Wording improvement suggested Proposed change: "The contract acceptor should permit ~~**the**~~ inspections ~~**of**~~ **by** the contract giver in connection with the ~~**sub**~~contracted activities
1035	Comment (Low Priority): The section heading does not include the word 'Complaints' (Not all complaints are quality defects and not all quality defects are identified via complaints)

Line number(s) of the relevant text	Comment and rationale; proposed changes
1037/ 1038	Comment (Low Priority): Additional text based on Eudralex Volume 4, 8.9 on elements to be covered as part of a quality defect investigation would be useful here. Proposed change: "**Complaints,** quality defects and product recalls"
1046	Comment (Low Priority): The statement that "The authorities should be informed in accordance with the relevant regulations" is vague. Proposed change: For clarity, suggest specific reference is made to the relevant regulations.
section 14.2 general	Comment: Additional information on product recall from EudraLex Volume 4, 8.20 – 8.31 could usefully be included here. Proposed change: E.g., more detail about "how the recalled material should be treated"; tracking the progress of a recall and its close out; testing effectiveness of arrangements.
1054-1056	In cases where the ATMP was already administered, the process for notification of the Health Care Provider and the competent authority should be addressed in both the clinical stage of development as well as for a marketed ATMP.
1057-1060	Biosafety – not to be dealt within this guidance