

Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

Cell Therapy Catapult comments

1. General comments on the document

How does the revision of Annex 1 of Eudralex Volume 4 fit with the intent and purpose of this guideline?

It is not clear how this guidance is to be used: as a supplement to Eudralex Volume 4 or to replace it as a standalone document for ATMPs. If as a supplement then the level of general detail is often a repeat of the existing content of Eudralex Volume 4 and therefore unnecessary, and if as a replacement we consider that this guideline is too detail-light to be useful as a standalone document and it should be used together with other GMP and ATMP guidelines.

It is not clear what the status of this guidance should be given that compliance with GMP (regarded as Eudralex Volume 4) is legally mandated in 2003/94/EC. Overall, we would recommend that the existing GMP guidelines and relevant Annexes continue to provide the over-arching requirements for manufacture of ATMPs. The draft document under consultation could be more appropriately presented as providing clarification and specific guidance on the application of the GMP guidelines to the manufacture of ATMPs.

In addition, it is important to consider inspections of facilities in the drafting of this guideline. If the proposed guidance is a standalone document, separate from Eudralex Volume 4, it is unclear how Medicines Inspectors from the member state competent authority will inspect. This is particularly the case for companies who may produce both ATMPs and non-ATMP medicinal products. Consequently, there is a potential for disparity between inspections in member states. To prevent such uncertainty we request that the guidance document, whether its final status is a stand-alone document or an Annex to Eudralex Volume 4, be approved by the Inspectors Working Group prior to finalisation.

The above notwithstanding, Cell Therapy Catapult welcomes the understanding that a risk-based approach is required during the development of a product and through the phasing of clinical trials, and we suggest that this is expanded upon and examples used as illustration.

Cell Therapy Catapult would welcome the chance to be involved in a user engagement session on the further development of this guidance. This meeting could be a forum for the discussion of issues as the users perceive them and to develop some worked examples for inclusion in the guidance note.

2. Comments addressing the questions in the document

GMPs for ATMPs: general principles

Q1: Are the principles laid down in Section 2 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.

Response

See the general comments above.

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.

Response

In addition to the general comments above, the risk-based approach referred to in Guideline EMA/CAT/CPWP/686637/2011; *Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products* is intended to justify the content of the MAA dossier in terms of development studies.

From the Risk-Based Approach guideline EMA/CAT/CPWP/686637/2011:

“The aim of the risk-based approach in the development of ATMPs is to determine 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 requirements of this Annex. The application of the risk-based approach in the preparation of a MAA dossier is optional.”

“It should also be differentiated from risk analysis such as it is used for medical devices or as part of quality management of ATMP production as described in ICHQ9 GMP guideline. The risk-based approach should also not be used to address risk-based quality management and risk factors, which are subject to principles of GMP, GLP and GCP.”

The appropriate references for consideration of risks associated with the manufacturing process are *ICH Q9 Quality Risk Management* within the context of *ICH Q10 Pharmaceutical Quality System* and *CBMP Guideline on Human Cell Based Medicinal products EMA/CHMP/410869/2006*, which states that *“A risk analysis approach can be used by the applicants to justify the development and evaluation plans and can be a basis for the preparation of a risk management plan.”*

The flexibility for ATMPs referred to in Section 2.1 should, therefore, be clearly distinguished from the formal Risk-Based Approach for ATMPs as set out in EMA/CAT/CPWP/686637/2011. We suggest that examples of the application of the risk-based approach for both manufacture and submissions should be provided.

Q3: How should the quality systems established in accordance with Directive 2004/23/EC 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?

Response

The Cell Therapy Catapult recognises that there is a spectrum of complexity of manufacturing processes for ATMPs and that those processes which involve minimal manipulation to produce an ATMP involve manufacturing processes of relatively lower risk, often very similar to processes which are routinely used to prepare non-medicinal products in hospitals, such as those used in haematopoietic stem cell transplant.

However, within the Regulation, the concept of a tissue-/cell-based product being regulated differently because it is for a “non-homologous” use involving minimal manipulation is at odds with the existing definition of “engineered” cells/tissues, which is an integral part of the definition of a somatic cell therapy (2001/83/EC) and a tissue engineered product (Regulation 1394/2007). As a consequence, minimally manipulated ATMPs for non-homologous use must be manufactured in accordance with GMP standards for medicinal products for human use.

The JACIE accreditation system, unlike Eudralex Volume 4, is not a recognised requirement for the manufacture of human medicinal products and therefore Medicines Inspectors would not inspect against this standard. The interface between the QMS required for donation, procurement and donor testing under 2004/23/EC, and the start of GMP requirements for manufacture of the ATMP, is already established in Eudralex Volume 4 Annex 2. Human tissues and cells, and tissue products derived from them that do not meet the definition of ATMPs, will be covered, for their subsequent processing, storage and distribution, by the existing provisions of 2004/23/EC and 2006/86/EC.

Cell Therapy Catapult would suggest therefore, given the existing Regulation, that rather than an adaption of standards for manufacture, it is the licensing and inspection of premises producing minimally manipulated and low-risk products for non-homologous use that should be considered in this document. For products considered lower risk, either because of their method of manufacture and/or their subsequent use, then the systems and procedures to support their manufacture can be less extensive than higher risk products. It would be very useful to provide examples of how such flexibility can be enacted in this document and in addition, Inspectors from the Competent Authorities should be trained in a risk-based inspection of such tailored QMS.

Personnel

Q4: Are the requirements laid down in Section 3 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.

Response

This section is redundant because it is a repetition of information contained in Eudralex Volume 4 but in less detail. We consider that this section could be removed from this guideline, subject to confirmation of the role of the guideline in respect of Eudralex Volume 4.

We would encourage the Commission to run an Interested Parties meeting to discuss the particular issues for ATMPs. As an example relating to personnel involved in the manufacture ATMP, SMEs and

academic and hospital units often have a limited pool of appropriately trained staff. Consequently, it may not be possible to have a separate QC and operational staff. In addition, these units often need to rely on contract or remote QPs. It is suggested that the proposed guideline provides guidance on issues such as these.

Premises

Q5: Are the requirements laid down in Section 4 sufficiently well adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

Response

This section is redundant because it is a repetition of information contained in Eudralex Volume 4 but in less detail. We consider that this section could be removed from this guideline, subject to confirmation of the role of the guideline in respect of Eudralex Volume 4. However, the guideline could discuss particular requirements of facilities. These facilities, often in academic/hospital based settings, have competing priorities including the production of autologous patient therapies that need to be delivered to suit both the patient needs (dependent on disease progression) and concomitant treatments/regimens. It is suggested that guidance on the use of best practice for segregation and line clearance would be particularly helpful to these groups.

Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?

Response

The Cell Therapy Catapult agrees that flexibility based on risk assessment is very important to ATMPs. It is noted that GMP already incorporates the requirement for a risk-based assessment of facility design and specific examples of how this can be applied to ATMPs would be very useful.

Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.

Response

The Cell Therapy Catapult agrees that flexibility based on risk assessment is very important to ATMPs. It is noted that GMP already incorporates the requirement for a risk-based assessment of facility design and specific examples of how this can be applied to ATMPs would be very useful.

The Cell Therapy Catapult believes that patient safety should be considered at all stages of a clinical trial and the facility should be designed to meet these safety requirements. The application of a risk based assessment (and inspection) should however allow for the GMP requirements to increase as the risk in patient exposure increases.

Production areas

Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)

Response

Because patient safety must always be ensured, we suggest that the choice of manufacturing environment should be based on risk to ensure that manufacturing process creates a safe product, rather than matched to the stage of clinical development. We consider that all open processes, in which the cells are exposed to the environment, should be conducted in a grade A environment with an appropriate background. In other cases, the background environment quality should be dependent on an assessed level of risk on a product and process-specific basis.

Equipment

Q9: Are the requirements laid down in Section 5 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Response

This section is redundant because it is a repetition of information contained in Eudralex Volume 4 but in less detail. We consider that this section could be removed from this guideline subject to confirmation of the role of the guideline in respect of Eudralex Volume 4, regardless of the format of the final document

Documentation

Q10: Are the requirements laid down in Section 6 sufficiently well adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.

Response

This section is redundant because it is a repetition of information contained in Eudralex Volume 4 but in less detail. We consider that this section could be removed from this guideline subject to confirmation of the role of the guideline in respect of Eudralex Volume 4.

Regarding additional flexibility for ATMPs, it should be recognised that some smaller manufacturing establishments might find certain documentation requirements, e.g. double sign-off on critical process steps, to be extremely burdensome. We suggest that as in all areas of GMP, a risk-based approach to justification of the operation of manufacturing facilities is appropriate.

We note that Section 6.5 (Retention of documents) requires some clarification because records for ATMPs must be retained for a minimum of 30 years. Therefore, the discussion around the 1- or 5-year retention period is irrelevant. The requirement for a 30-year document retention period in the ATMP Regulation arises from the requirements for donor record retention in 2004/23/EC and 2002/98/EC, and these Directives should be referenced for transparency. We believe that the 30-year retention policy is excessive but recognise that a formal revision of the relevant legislation would be necessary to address this requirement. We suggest that revision of the retention period, and convergence with US and Japan requirements, is considered if this legislation is to be revised. It would also be helpful to provide more practical guidance on which documentation is required to meet the traceability requirements, as this can be uncertain for developers new to the ATMP field as discussed in the question below.

In addition, guidance specific to ATMPs which includes specific emphasis on the obligations of the hospital site to maintain full traceability of the product from receipt to administration would be advantageous because many clinical practitioners are not aware of this responsibility.

Q11: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?

Response

Full GMP and 30 years traceability documentation will be required in accordance with 2001/83/EC and 2003/94/EC. A risk-based approach to the level of detail of these documents can be adopted if justified. Such a risk-based approach is permitted under current GMP rules. We suggest that this guidance document is expanded to include examples of this. Interested parties could be invited to provide examples in line with the revision of this document.

Q12: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.

Response

As mentioned above, the requirement to assess all aspects of production for risk provides for adequate flexibility in individual circumstances.

Starting and raw materials

Q13: Are the requirements laid down in Section 7 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Response

We suggest that the discussions around starting materials and raw materials could be separated to prevent confusion about the specific requirements for each. The definitions should be stated consistent with the content of 2001/83/EC Annex Part IV. Reference should be made to the European Pharmacopoeia general chapter 5.2.12 on raw materials for the production of cell and gene therapy

products. Additionally, guidance on what starting materials and raw materials are, and how to perform a risk assessment regarding their suitability for use, would be helpful.

Specific Points

Lines 448–449 may need further explanation because human tissue/cell starting materials need to be procured and deemed suitable for use according to the EU Tissues and Cells Directives.

Further clarification is also needed on whether viral vectors are classified as raw materials, starting materials or active pharmaceutical ingredients.

The discussion of raw materials on lines 450–454 may benefit from additional information on auditing of suppliers of raw materials and continuity of supply and specifically how risk assessment can be applied to determine the needs to audit a supplier in early clinical trial phases.

We note that the statement on lines 466–469 that licensed blood and tissue establishments do not require auditing by ATMP manufacturers is appropriate. This incentive is welcomed but is contradictory to the GMP guidelines so as such needs to be agreed by all Inspectorate branches of NCA.

Line 485: the recommendation that raw and starting materials should be heat-sterilised, and then adding a requirement for viral inactivation by gamma sterilisation, seems unnecessarily burdensome. Some materials can be appropriately sterilised and inactivated using the same irradiation process whilst others are not suitable for such treatment.

Line 493: human tissue/cellular starting materials should, from April 2017, be coded in accordance with Directive 2015/566. This requirement should be included in the section on labelling.

Line 511: the interface and delineation of responsibilities between the ATMP manufacturer and tissue/blood establishments need clarification throughout. In some parts of the text, the overall responsibility for blood/tissue starting materials appears to be placed on the ATMP manufacturer, and in others, the existence of an appropriate tissue/blood establishment licence appears to be considered sufficient.

Overall, the document should consider separating out requirements for human tissues and cells from those for other raw and starting materials.

Seed lot and cell bank system

Q14: Are the requirements laid down in Section 8 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.

Response

The manufacture of cell banks is not always necessary for ATMPs and this should be made clear. However, where the manufacture of cell banks is necessary, we consider that reference to ICH guidelines Q5D and Q5A is very important. Discussion on cell banks for both viral vector production and cell-based medicinal product manufacture would also be useful. Some guidance could also be provided on the obligations of manufacturers when a new master cell bank is required following the granting of a marketing authorisation.

The term “cell stock” is introduced in the document (line 529), presumably as a means of distinguishing a relatively small bank of expanded cells from the conventional MCB/WCB system usually employed for production of conventional biological products. However, its use is not consistent in the text: in some places it appears to be used interchangeably with “cell bank” and in others to denote something other than a cell bank. Terms should be clarified.

Line 541: the text on management of changes in the MA should be beyond the scope of a guideline on GMP.

Production

Q15: Are the requirements laid down in Section 9 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials)? Please provide comments on the text below as appropriate.

Response

The discussion around critical operational parameters in lines 575–579 is somewhat confusing regarding the requirements for investigational versus licensed products, and additional information to clarify this would be considered useful (including the requirements for IMPs at different stages of clinical development).

Section 9.2 may benefit from additional discussion of the traceability requirements for human starting materials.

The information in lines 604–605 is inappropriate to human starting materials.

Line 618: “mix up” should be prevented for all materials, not just autologous materials.

Line 637: the use of closed systems is not always possible for certain ATMPs.

Lines 640–645: we suggest that discussion of viral vectors and GTMPs is addressed in a separate section for clarity.

Lines 648–649: the extent of cleaning validation expected between the manufacture of different batches of CBMPs should be clarified.

Lines 666–668: clarification of what the “special considerations” for continuous culture are should be provided.

Line 687: guidance on quarantine procedures would be helpful. In the case of short shelf-life ATMPs it is not always possible to quarantine them until final QP release. Such products will frequently need to be administered to the patient before final sterility test results, for example, are available. It would be appropriate to add guidance on requirements for cryopreservation and storage of finished products.

Lines 691–693: we note that recall of ATMPs is often not possible, e.g. when a single batch is made for and administered to an individual patient, and so the implications of additional donor health information on the use of the product and monitoring of the patient should be clarified.

Lines 698–707: we note that this information is largely inappropriate for ATMPs because reprocessing is not expected and single batches manufactured for individual patients will not be returned.

The scope of QMS and licensure requirements in situations where additional handling of the ATMP is required at the clinical site, e.g. thawing, diluting, re-suspending, loading into delivery systems, should

once more be approached from a risk-based approach and Cell Therapy Catapult would welcome some consideration to be given to flexibility of licensure requirements for low risk medicinal products.

Qualification and validation

Q16: Are the general principles laid down in Section 10 sufficiently well adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials)? Please provide comments on the text below as appropriate.

Response

Lines 714–716 illustrate the insufficiency/inadequacy of the text as a replacement for existing GMP guidelines: Eudralex Volume 4 Annex 1 provides detail on the conduct and acceptance criteria for an aseptic process validation, whereas the text of the consultation document does not include any such detail, e.g. tabulation of different requirements for different process types.

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.

Response

Cell Therapy Catapult particularly welcomes the opportunity to comment on this point as it represents a critical and especially challenging area of ATMP development. Many ATMPs are autologous and must be produced from a very small sample of starting tissue/cells, making a conventional approach to process validation impractical at best. Different materials will require different approaches based on their availability and specific characteristics, for example:

- Adult allogeneic cells/tissues from a healthy donor, expanded and banked
- Cells differentiated from an established stem cell line (e.g. embryonic, iPSC)
- “Normal” cells/tissues from an autologous donor, which may be unlimited (e.g. adipose-derived MSCs) or more restricted (e.g. bone marrow-derived), for tissue regeneration
- “Diseased” cells/tissues from an autologous donor (e.g. CD34+ for production of a gene therapy for a monogenic disorder)

It cannot be assumed that large quantities of material will be available for process development and validation purposes, and therefore a pragmatic approach based on analysis of the risks and critical steps of the process must be used. The following suggestions are provided in this respect:

Cell lines. Standard approach to process validation, with extent appropriate to development stage.

Autologous “normal” cells/tissues. The availability of these materials will be tissue-specific to an extent. Material from bone marrow aspiration will be available in smaller quantities than e.g. adipose-derived cells. The use of surrogate material could be considered, for example bone marrow from elective hip replacement surgery. The comparability of surrogate starting material from different sources (donor age, existence of disease, anatomical source, e.g. femur vs iliac crest) should be evaluated. The process validation approach will need to be graduated depending on the quantities of tissue/cells available, and should focus on gaining maximum experience of the process from each run/replicate. The overall approach should include development of understanding of the likely range of values expected in the process from the cell type involved.

Allogeneic tissues/cells. Process validation of initial steps (e.g. isolation from tissue/aspirate/blood, initial expansion to MCB stage) will be subject to similar limitations as for autologous cells. From the MCB stage onwards, a more conventional process validation approach can be anticipated. If limited expansion is undertaken, process validation activities could potentially be conducted on cells at a higher passage number than intended for clinical use once the effect of expansion on cell characteristics has been determined.

“Diseased tissues/cells”. Products based on modification of autologous cells to treat a genetic disorder will entail the use of cells from patients having the disorder in question. The starting material will therefore be extremely limited and process validation using these cells may need to be limited to those parts of the process that focus on the genetic modification itself. Other aspects such as expansion, packaging etc could potentially be validated using a representative surrogate cell type.

This is an area in which a staged approach could be appropriate because early clinical trials may not require a fully validated manufacturing process, as is currently the case for traditional medicinal products. In all cases, the approach to process validation should be based on demonstrating that it is fit for purpose. In particular, reduced process validation should, wherever possible, be offset by in-process testing to allow for assessment of comparability of product with that produced later in development.

Qualified person and batch release

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

Response

1. Role of the Qualified Person

QP release of medicinal products against the national Member State laws for manufacture and the detail lodged with the CA as part of a CTA or MAA is a legal requirement. Given the short shelf life of many ATMPs, a two-stage QP certification in which the product is initially released against manufacturing and in-process control test results, with final sign-off after receipt of longer duration release testing (e.g. sterility tests) is often necessary.

Similarly, it may be necessary to permit release of the product by a QP who is not present at the final manufacturing site. The specific circumstances applicable to many ATMPs in development and use in hospitals mean that an ATMP may need to be released at a hospital site rather than a conventional manufacturing site. Examples include a minimally manipulated ATMP intended for non-homologous use that is prepared using a commercial cell separation/preparation device, or thawing and re-suspension of cells prior to combining them with other materials at the point of administration.

The guideline could usefully include recommendations for best practice in both of these areas.

2. Batch Release

Line 753: use of the term “must” is inappropriate in terms of mandatory re-testing when the subsequent provisions allow for acceptance of test results from the third country. It should be noted here and elsewhere (e.g. lines 755, 875) that it is not always possible to separate the testing of active

substance of an ATMP from the finished product and that therefore, with appropriate justification, testing of both can be combined into a single set as authorised in the CTA/MAA.

Line 757: limited shelf life is also a key limitation on the potential for re-testing upon import into the EU.

Line 805: medical devices should comply with relevant essential requirements of the MDD. Not all ERs are applicable to every medical device; it is the responsibility of the MA/CTA holder to determine which ERs apply to the medical device in the context of its intended use in the combined ATMP.

Lines 832–840: should the retention of the register for ATMPs, and release certification for ATIMPs, be 30 years, in line with other record retention requirements?

Quality control

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

Response

Regarding the independency of quality control staff from production staff discussed in Section 12.1, General Principles (lines 894–896), we note that this is not always possible in small organisations and some overlap in roles may be necessary. In this respect, independence can be achieved procedurally and via detailed job responsibility matrices.

Section 12.2, Sampling, would be more useful with better guidance, e.g. can examples of sampling schemes for different starting materials (autologous versus allogeneic) and raw materials be provided? In addition, the discussion presented can be interpreted to refer incorrectly to raw materials as starting materials (e.g. line 938). This is also the case in Section 12.3, Testing, where line 954 states that identity testing of starting materials is needed. Clarification on what is expected and needed here is required. Also in this section, line 957 states that testing methods should be qualified/validated, but this applies to equipment too.

Section 12.4 discusses the stability monitoring program for a medicinal product post-MAA, but stability testing needs to be introduced during development and this should additionally be discussed. The guidance needs to recognise that for some autologous products conventional stability testing programmes are not possible and that alternative provisions need to be made. For example for very short shelf-life products, the transport validation should include specification testing at the end of shelf-life to ensure acceptable quality, viability, potency etc.

Outsourced activities

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

Response

Section 13.1, General Principles, only discusses outsourced manufacturing activities, but other activities (e.g. quality control) may also be outsourced and should be mentioned.

The guideline should clarify that it is not mandatory to qualify alternative suppliers for all materials.

Quality defects and product recalls

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

Response

We note that product recalls are not possible for some ATMPs (e.g. a single batch manufactured for an individual patient that is administered before final product release testing results are available). This implies the need for greater emphasis on manufacturing, quality assurance and pre-release testing. The guideline could usefully include recommendations on regular reviews of product quality to support ongoing adequacy of the process and product. Specific guidance on how quality defects for such products should be acted upon is considered helpful. The guidance should include the option for documented destruction of defective product at the clinical site, where appropriate, as an alternative to return of product.

The requirement for retention samples should be addressed in the guideline: it is frequently meaningless to attempt to retain ATMP samples for testing when shelf life is measured in days. Flexibility in this aspect of GMP is considered to be essential. Similarly, the requirements for reference materials should be reconsidered for ATMPs and appropriate guidance on justification for absence of reference materials should be included.

Environmental control measures for gene therapy products

Response

We consider that this section is covered sufficiently in the relevant sections of Volume 4 and its respective annexes.

Detailed guidance, perhaps separate from the GMP guideline under review here, on requirements for GMO assessments in each Member State would be very useful. The current lack of clarity on data requirements and procedures is a major problem for gene therapy developers and is a source of delay in clinical trial approvals. In the absence of harmonisation of GMO requirements across the EU, some increased transparency of national requirements would be a significant benefit for this sector. It is suggested that guidance on national bodies responsible for the approval for the use of GMO, documentation requirements and processes could be included as an appendix to the proposed guidance document.

Reconstitution of product after batch release

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

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

Response

The specific requirements for some ATMPs mean that they may require some processing immediately prior to use in the hospital. These processes may include thawing and perhaps dilution with a pre-specified volume of liquid for administration. We agree that processes defined as “reconstitution” (although this may not be the best term) should be validated by the manufacturer/MA holder, and detailed information provided to ensure a standardised approach. Training of users should be considered as a part of the Risk Management Plan for the product.

A balance between pragmatism and safety is essential to achieve patient safety without unnecessarily hindering the introduction of new medicines. The guidance in this area should emphasise the need for a clear demarcation of responsibility between the clinical/reconstitution site and the clinical trial sponsor/MAH.

The scope of QMS and licensure requirements in situations where additional handling of the ATMP is required at the clinical site, e.g. thawing, diluting, re-suspending, loading into delivery systems, should once more be approached from a risk-based approach and Cell Therapy Catapult would welcome some consideration to be given to flexibility of licensure requirements for low risk medicinal products.

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

Response

Reconstitution is an accepted necessity in the preparation of numerous medicines and should be permitted, where justified, for ATMPs. The key will be to appropriately define what activities can be considered reconstitution (see Q24): if the approach is too restrictive this will represent a significant barrier to the use and authorisation of otherwise useful medicines, but if too lax, there is a potential for lack of control over important manufacturing steps that can have a major impact on product quality.

Q24: What activities should, in your view, be considered as reconstitution?

Response

Reconstitution should be limited to the preparation of the ATMP for administration to the patient, e.g. thawing and diluting into a vehicle. It should be restricted to those steps which can be validated and easily undertaken by clinic staff. Steps requiring adaptation of the dosage (number of cells) could be considered reconstitution if the processing step was relatively simple and within a closed system. Given the different types of potential manipulations that could be required for different ATMPs, the principal applications of this term are envisaged to be thawing and dilution as for other medicines. Other operations necessitated by the specific requirements for an individual ATMP, for example open handling of the cells or combining with a delivery device, should be scientifically justified on the basis of a risk analysis of the steps concerned and their potential impact on patient safety and product quality. Training of staff and validation of the in-clinic procedures, and allocation of responsibility

between the QP, the MAH/sponsor and the hospital site, should be described in detail in the CTA/MAA as appropriate.

Automated production of ATMPs

Devices that permit the selection and/or manipulation of cells are emerging. Often these devices are intended to be used in hospitals. The automated production of ATMPs through these devices poses specific challenges.

Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?

Response

The regulation of ATMPs produced by automated devices represents a fundamental challenge to the established paradigm for medicinal products. On the assumption that no change is anticipated to the legal definition of cell therapy/tissue engineering products in Directive 2001/83/EC and Regulation (EC) No 1394/2007, it should first be reiterated that “non-homologous” use of cells causes them to be classified as an ATMP even if only minimal manipulation has occurred.

The authorisation of such products needs to be addressed elsewhere, but from the GMP perspective, there will need to be recognition of the issues raised. There is clearly a medical need to be able to process cells and tissues such as bone marrow aspirate/adipose tissue in theatre using purpose-designed devices. The use of automated machines to produce clinically acceptable materials for re-infusion into a patient is well established; for example, the use of apheresis machines throughout the EU. This model may be a useful part-analogy. In terms of responsibility, the hospital should have responsibility for tissue procurement, operation of the automated processing system, and administration to the patient. The hospital should also take responsibility for ensuring that all staff operating the device have been fully trained to do so. The device manufacturer is required to provide full instructions for use as part of the CE-marking process for the device; in the context of use of the device to produce therapeutic products, the manufacturer could be required to provide training and certification in the correct operation of the device.

Entirely closed systems would generally not require a graded cleanroom environment for their safe operation, but certain elements of GMP should still be applicable. For example, user training, records and traceability, labelling, product/sample segregation requirements should be observed. The requirement for QP release should be addressed in the guidance, particularly with regard to testing of the ATMP.

As detailed above, we believe that the scope of QMS and licensure requirements for such preparation steps should be reviewed with a view to the introduction of a risk-based licensing system for sites where activities are undertaken which may be considered manufacturing or processing in accordance with 2001/83/EC and 2003/94/EC, but may instead be considered simple preparation steps.