Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

The sole purpose of this consultation is to collect relevant evidence and information from stakeholders to help the Commission develop its thinking in this area.

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

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1. Introduction

Compliance with Good Manufacturing Practice ("GMP") is essential to ensure the quality of medicinal products. The intrinsic characteristics of Advanced Therapy Medicinal Products ("ATMPs") (such as variability of the starting materials, small batch sizes, short shelf-life, *etc.*) pose specific challenges for the manufacturing process. Additionally, early phases of research may take place in a hospital setting operating under a quality system different from the quality system typical of the pharmaceutical sector.

Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products (hereinafter "ATMP Regulation")[1] provides for the development of Guidelines on Good Manufacturing Practice specific to ATMPs.

This consultation document is intended to seek the views of stakeholders regarding the GMP requirements that should be applied by manufacturers of ATMPs for commercial distribution in accordance with the terms of a marketing authorisation ("commercial ATMPs"), as well as by manufacturers of ATMPs to be used in clinical trials ("investigational ATMPs"). Manufacturing of ATMPs under the hospital exemption is not within the scope of this consultation document.

2. 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.

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.

Q3: How should the quality systems established in accordance with Directive 2004/23[2] 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?

[1] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L324, 10.12.2007, p.121).

[2] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

Due to their intrinsic characteristics, quality plays a major role in the safety and efficacy profile of ATMPs. It is the responsibility of the ATMP manufacturer to ensure that the manufacturing process is adequate to safeguard the quality of the product (so-called "pharmaceutical quality system"). Compliance with GMP is an essential part of the pharmaceutical quality system.

The main objectives of GMPs are that:

- the personnel is adequately trained and there is clear allocation of responsibilities;
- the premises and equipment are suitable and that there is appropriate maintenance thereof;
- there is a good documentation system that ensures that appropriate specifications are laid down for starting and raw materials, as well as intermediates and bulk products, that the production process is clearly understood, and that appropriate records are kept;
- the production process is adequate to ensure the quality of the product, that measures are in place to identify any process deviation, and that appropriate action is taken in such cases;
- there is a quality control system which is independent from production;
- quality defects are identified as soon as possible, the causes investigated, and appropriate measures are taken.

Self-inspections should be conducted to monitor compliance with GMP and the specific requirements provided for in the marketing authorisation or clinical trial authorisation and to implement corrective measures where appropriate.

No provision in the GMP Guidelines (including the risk-based approach) can be regarded as derogation to the terms of the marketing authorisation or clinical trial authorisation. The manufacturing requirements (*e.g.* specifications, manufacturing process, controls, *etc*.) foreseen in the marketing authorisation or clinical trial authorisation should always be adhered to.

2.1. Risk-based approach

ATMPs are complex products and risks may differ according to the type of product. For example, the risks to the quality of the product are greater when there is a complex manufacturing process. It is also acknowledged that the finished product may entail a high degree of variability due to the use of biological materials and complex manipulation steps (*e.g.* cultivation of cells). In addition, the manufacture and testing of autologous ATMPs poses specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process and of the product in practice.

It follows that it is important to recognise some flexibility in the application of the GMP requirements so that the ATMP manufacturer can implement the measures that are most appropriate having regard to specific characteristics of the manufacturing process and of the product. Any flexibility applied must, however, be compatible with the need to ensure the quality of the product.

The production of investigational ATMPs involves added complexity in comparison commercial products (*i.e.* products with a marketing authorisation) due to the often incomplete knowledge about the product (*e.g.* potency or toxicity) as well as the lack of fixed routines. ATMPs are also often developed in an academic or hospital setting operating under quality systems different to those typically required for the manufacture of conventional medicinal products. While an acceptable level of quality must be ensured for investigational ATMPs, it is acknowledged that additional flexibility is warranted, in particular for early phases of clinical trials.

In turn, the risk-based approach also implies that the manufacturer is responsible to put in place additional measures (beyond those suggested in the GMP Guidelines) if that is necessary to address the specific risks of the product.

When identifying the control measures that are most appropriate in each case, the ATMP manufacturer should consider all the potential risks.

3. 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.

The ATMP manufacturer should have an adequate number of personnel with the necessary qualifications and adequate practical experience relevant to the intended operations.

All personnel involved in the manufacturing or testing of an ATMP should have a clear understanding of its tasks and responsibilities.

There should be appropriate training in the requirements specific to the manufacturing and testing of the product as well as detailed hygiene programs. Personnel working in areas where contamination is a hazard should be given specific training. Cleaning and maintenance personnel should also receive specific training in particular on measures to avoid risks to the product, to the environment, and health risks.

Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

Steps should be taken to ensure that health conditions of the personnel that may be relevant to the quality of the ATMP are declared. As far as possible, no person affected by an infectious disease or having open lesions on the exposed surface of the body should be involved in the manufacture of the product.

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.

Where required to minimise the risk for cross-contamination, restrictions on the movement of all personnel should be considered. In general, personnel should not pass directly from areas where there is exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, appropriate control measures should be applied.

Because of their essential role in the quality system, the person responsible for production, the person responsible for quality control and the Qualified Person ("QP") should be appointed by senior management. The roles and responsibilities of key personnel should be clearly defined and communicated within the organisation. Responsibility for production and for quality control cannot be assumed by the same person.

4. 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.

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?

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.

4.1. General principles

Premises must be suitable for the operations to be carried out. In particular, they should be designed to minimise the opportunity for cross-contamination, the risk of errors and, in general, any adverse effect on the quality of products.

Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and risk of cross-contamination that should be taken into account as part of the development of an overall strategy to minimise risks. This strategy should be used as a basis for the design of the premises and equipment.

It is important that the following general principles are implemented:

(a) Premises should be kept clean (disinfection to be applied as appropriate).

(b) Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products.

(c) Lighting, temperature, humidity and ventilation should be appropriate to ensure that they do not adversely affect the medicinal products, or the functioning of equipment.

(d) Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

(e) Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a transit area by personnel who do not work in them.

(f) The manufacture of technical poisons, such as pesticides and herbicides, or cytotoxic agents, should not be allowed in premises used for the manufacture of ATMPs.

4.2. Production areas

4.2.1. Design and construction

Dedicated production areas should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. In particular, to protect the operator and the environment, dedicated production areas should always be used for the manufacture of pathogenic organisms (*i.e.* Biosafety level 3 or 4).

Manufacture in a multi-product facility may be acceptable where appropriate risk-mitigation measures commensurate with the risks are implemented to prevent cross-contamination. Examples of such possible risk-mitigation measures include the use of closed systems, the use of self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning systems, campaign-based manufacturing, or implementation of adequate cleaning and decontamination procedures including the heating, ventilation and air condition systems. Further details are available in Section 9.3.

It is recommended that the design of the premises permits the production to take place in areas connected in a logical order corresponding to the sequence of the operations and required level of cleanliness. Likewise, the arrangement of the working environment, and specifically of the equipment and materials, should minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

The laid out of the premises should permit the separation of flows of contaminated materials and equipment from those sterilized/non-contaminated. Where this is not possible, the handling of contaminated materials/equipment should be separated in time.

Production areas should be effectively ventilated, with air control systems (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them, and to the external environment.

4.2.2. Aseptic environment

Premises should be appropriate and adequately controlled to ensure an aseptic environment for manufacturing of ATMPs. Special attention should be paid to products for which there is no sterilisation of the finished product. 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 possible, particular attention should be paid to the filling process. For commercial production of ATMPs, the premises should be fully validated.

The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the specific risks of the product and manufacturing process. Checks to detect the presence of specific microorganisms in the environment (*e.g.* host organism, yeast, moulds, anaerobes, etc.) should be performed where appropriate.

Air handling units should be designed, constructed, and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Depending on specific risks of the product, the use of single pass air systems should be considered.

Positive pressure areas should be used to process sterile products and for aseptic manufacturing but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (*e.g.* pathogens) they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings.

Clean areas should be supplied with air which has passed through filters of an appropriate efficiency. Clean air devices should be classified in accordance with ISO 14644-1. In general, an A grade with a background of B grade is required for pivotal clinical trials and commercial production.

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.)

Air vent filters (HVAC) used for large scale production should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals taking into account the specific risks.

Clean areas or clean/contained areas should be accessed through an air lock with interlocked doors.

4.2.3. Drains

In the case of large scale production, drains should be of adequate size, and have trapped gullies. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection. Developers are reminded that, for risks relating to biohazard waste, local regulations should be followed.

Clean areas should not have drains installed.

4.2.4. Lighting

Production areas should be well lit, particularly where visual on-line controls are carried out.

4.3. Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

Storage areas should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (*e.g.* temperature, humidity) these should be specified and monitored.

Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

Highly reactive materials or products should be stored in safe and secure areas.

4.4. Quality control areas

Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

Quality control laboratories should normally be separated from production areas. Further details are available in Section 12.1.

4.5. Ancillary areas

Rest and refreshment rooms should be separate from production, storage and quality control areas. Toilets and washrooms should not directly communicate with any of those.

Premises where laboratory animals are kept should be well isolated from production, storage and quality control areas with separate entrance and air handling facilities.

5. 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.

Manufacturing equipment should be suitable for its intended purpose and it must be adequately maintained. Repair and maintenance operations should not present any hazard to the quality of the products.

Manufacturing equipment should not present any hazard to products. Parts of production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

The equipment must be cleaned appropriately in order not to be a source of contamination. Single-use disposable material should be used, where possible. Sterilisation of multi-use equipment coming into contact with the product should be validated.

Primary containment should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

The performance of the measuring, weighing, recording and control equipment should be controlled by appropriate methods at defined intervals. Adequate records of such testing should be maintained.

Automatic, mechanical or electronic equipment, including computers shall be routinely calibrated, inspected or checked to ensure proper performance. Written records of those checks shall be maintained.

There should be sufficient controls to prevent unauthorised access to changes to data. Changes to data should be traceable (*i.e.* previous entry, date of change and identity of the person that introduced the change).

Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

6. 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.

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?

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.

6.1. General principles

Good documentation is an essential part of the quality assurance system and is key element of GMP. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly may affect the quality of medicinal products. Records required to ensure traceability should also be kept.

There are two primary types of documentation relevant for the quality assurance system: instructions (*e.g.*, specifications, SOPs, technical requirements, contracts) and records/reports.

Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. When electronic, photographic or other data processing systems are used, stored data should be protected against loss or damage, *e.g.* by methods such as duplication or back-up and transfer to another storage system.

Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents throughout the retention period.

A site master file should be prepared for every site involved in commercial manufacturing. The site master file should provide a high level description of the premises, activities conducted at the site and of the quality system implemented.[3]

6.2. Product Information

The instructions relevant to the manufacture of the medicinal product as well as relevant records/reports should be kept and be made available upon the request of the authorities.

6.3. Instructions

The specifications for the materials to be used, as well as the instructions that should be followed to manufacture the product, should be documented appropriately. These documents should be clear and detailed enough so as to ensure that there is consistent manufacture (appropriate to the relevant stage of development) and that the product complies with the required quality and relevant specifications.

Specifications and instructions should be periodically re-assessed during development and be updated as necessary. Each new version should take into account the latest data, current technology used, as well as regulatory requirements. It should also allow traceability to the previous document. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and documented. It is recalled that changes into the manufacturing requirements approved as part of the marketing authorisation must be agreed by the competent authorities and that substantial modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities.

As a minimum, the following should be documented:

(i) Written request to start manufacturing a batch (manufacturing order).

(ii) Specifications for raw materials, including:

- Instructions for sampling and testing, as appropriate. For investigational ATMPs, the manufacturer may rely on the certificate of analysis of the supplier if this is considered appropriate having due regard to the risks.
- Quality requirements with acceptance criteria.
- Maximum period of storage.
- For raw materials of biological origin, the source, origin, traceability and suitability for the intended use should be described. Contracts and quality requirements agreed with third party suppliers should be kept.

(iii) Specifications for starting materials, including:

[3] ATMPs manufacturers may follow the principles laid down in http://ec.europa.eu/health/files/eudralex/vol-4/2011_site_master_file_en.pdf.

- Source, origin and suitability for the intended use should be described. Contracts and quality requirements agreed with third party suppliers should be kept.
- Quality requirements with acceptance criteria and testing instructions.
- Storage and transport conditions and precautions.
- The maximum period of storage.
- Instructions to ensure the traceability of the starting materials, including substances coming into contact with the cells or tissues.

(iv) Specifications for intermediate and bulk products should be available where applicable.

(v) Batch definition.

(vi) Manufacturing instructions.

(vii) Specifications for finished products, in particular:

- Name/identification of the product.
- Description of the pharmaceutical form.
- Instructions for sampling and testing.
- Qualitative and quantitative requirements with acceptance limits.
- Storage and transport conditions and precautions.
- The shelf-life.

(viii) Release and rejection criteria for raw and starting materials, intermediates, bulk and finished product, including release strategy for characterisation results that are not available prior to product release.

(ix) Packaging instructions for each product. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. It is advised that the number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliations should take place to ensure that the correct quantity of each product required has been accounted for at each stage of processing.

(x) Instructions for product preparation for administration if applicable, *e.g*, thawing procedure.

6.2.2. Records/reports

Records should demonstrate that the relevant instructions have been complied with. Any significant deviations should be recorded and investigated, and appropriate corrective measures should be taken. The records should also enable the entire history of a batch to be traced.

The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch. Where different manufacturing steps are carried out at different locations

under the responsibility of different QPs, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

As a minimum, the following should be documented:

(i) Receipt records for each delivery of raw materials, starting material, bulk, intermediate as well as primary packaging materials. The receipt records should include:
- name of the material on the delivery note and the containers as well as any "in-house name" and or code if appropriate;
- supplier's name and manufacturer's name;
- manufacturer's batch or reference number;
- total quantity received;
- date of receipt;
- batch number assigned after receipt; and
- any relevant comment.

(ii) A batch processing record should be kept for each batch processed; it should contain the following information:
- name of the product and batch number;
- dates and times of commencement, of critical intermediate stages and of completion of production;
- quantities and batch number of each starting material;
- identification (initials) of the operator who performed each significant step and, where appropriate, of the person that checked these operations;
- a record of the in-process controls and identification (initials) of the person(s) carrying them out, as well as the results obtained;
- the product yield obtained at relevant stages of manufacture;
- copy of approved label;
- notes on special problems including details, with signed authorisation for any deviation from the manufacturing instructions;
- results of release testing and identification (initials) of the person(s) carrying them out; and
- traceability records from the sourcing of starting and biological raw materials to the finished product.

Note: Where a validated process is continuously monitored and controlled, manufacturing data might be limited to automatically generated compliance summaries and exception/out of specification data reports.

6.4. Other documentation

There should be appropriate documentation of policies and procedures to be applied by the manufacturer with a view to safeguard the quality of the product, including:

(i) Qualification or validation of processes, analytical methods, equipment and premises.

(ii) Investigations into deviations and non-conformances.

6.5. Retention of documents

Batch documentation should be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the QP, whichever is the longest. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

Critical documentation, including raw data (for example relating to validation or stability), which supports information in the marketing authorisation should be retained whilst the authorization remains in force. However, it is acceptable to retire certain documentation (*e.g.* raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation.

For cell-based products, data ensuring the traceability of the finished product, its starting and raw materials, including all substances coming into contact with the cells or tissues, should be kept for a minimum of 30 years after the expiry date of the product, unless a longer period is foreseen in the marketing authorisation.

7. 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.

The quality of starting and raw materials is a key factor to consider in the production of ATMPs. Particular attention should be paid to avoid contamination and to minimise as much as possible the variability of the starting and raw materials. Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked (identity, temperature control, *etc*).

Only starting materials which have been released by the person/department responsible for quality control should be used.

Raw materials should be of suitable quality having regard to the intended use. Where possible, raw materials used in the manufacturing of ATMPs should take into consideration the *Ph. Eur general chapter on qualification of raw materials for cell and gene transfer product production.* The ATMP manufacturer should put in place appropriate measures to ensure that raw materials can be traced in order to facilitate recall of products if necessary.

The donation, procurement and testing of human tissues and cells of used as starting materials or raw materials (*e.g.* feeder cells) should be in accordance with Directive 2004/23/EC. For materials that are outside the scope of the Directive, the ATMP manufacturer should take appropriate steps to ensure the quality, safety and traceability thereof.

The ATMP manufacturer should establish quality requirements for the starting materials (specifications) which should be agreed with the supplier(s). These specifications should cover aspects of the production, testing and control, and other aspects of handling and distribution as appropriate. The specifications set should be in compliance with the terms of the marketing authorisation or clinical trial authorisation.

The ATMP manufacturer should verify compliance of the supplier with the agreed specifications. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials. Blood establishments and tissue establishments authorised and supervised under Directive 2002/98[4] or Directive 2004/23 do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing.

In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting material, in particular, on tests results performed by the supplier and traceability data.

The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.

Appropriate measures should be put in place to protect the product and the preparation of solutions, buffers and other additions from the risk of contamination (or within the accepted bioburden level foreseen in the marketing authorisation/clinical trial authorisation). For cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, it is particularly important to take appropriate measures to ensure the quality of starting and raw materials.

Where sterilization of starting materials (*e.g.* chemical matrixes) and raw materials and excipients is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (*e.g.* irradiation and filtration).

[4] Directive 2002/98 of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

The use of antibiotics may be necessary to reduce bioburden associated with procurement of living tissues and cells. When antibiotics are used, they should be removed as soon as possible. Additionally, it is important to ensure that antibiotics do not interfere with the sterility testing, and that they are not present in the finished product.

Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

- the designated name of the product and the internal code reference (if applicable);
- a batch number given at receipt;
- where appropriate, the status of the contents (*e.g.* in quarantine, on test, released, rejected);
- where appropriate, an expiry date or a date beyond which retesting is necessary.

Bulk containers from which samples have been drawn should be identified.

Where the test(s) required to release the starting materials take a long time (*e.g.* sterility test), it may be permissible to process starting materials before the results of the test(s) are available. The risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed. In such cases, the finished product can only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are possible (*see* also section 11.3.2).

With a view to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers, starting materials should only be dispensed by designated persons. Each dispensed material and its weight or volume should be independently checked and the result recorded.

The initial processing of starting material has to take place in accordance with the pharmaceutical rules,[5] even if it is outsourced to a third party (*e.g.* to a tissue establishment). This means that the overall responsibility for the quality of the starting materials lies with the ATMP manufacturer.

8. 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.

As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under appropriate conditions. This should include an appropriately controlled environment to protect the seed lot and the cell

[5] Donation, procurement and testing of cells and tissues are governed by Directive 2004/23/EC . These activities are not to be considered as processing of starting materials.

bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (*e.g.* virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the marketing authorisation/clinical trial authorisation.

For stages prior to the master seed or cell bank generation, documentation should be available to support traceability including issues related to components used during development with potential impact on product safety (*e.g.* reagents of biological origin) from initial sourcing and genetic development if applicable.

Following the establishment of cell stocks, cell banks and master and viral seed lots, quarantine and release procedures should be followed. Evidence of the stability and recovery of the stocks, seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination (*e.g.* stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take account the infectious nature of the materials to prevent cross-contamination.

Cell-based products are often generated from a cell stock obtained from limited number of passages. In contrast with the two tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be addressed in the marketing authorisation and the conditions therein should be complied with.

Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.

The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot/cell bank management system, the containers should not be returned to stock.

In exceptional and justified cases, it might be possible to accept the use of cell stocks/cell banks and viral seed stocks that were generated without full GMP compliance. In these cases, the lack of GMP compliance may require additional testing to ensure proper quality of the starting material. In all cases, the overall responsibility for the quality lies with the ATMP manufacturer.

9. 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.

9.1. General principles

Production operations, including filling and packaging, should follow clearly defined procedures designed to ensure the quality of the product, consistent production (appropriate to the relevant stage of development), and to comply with the requirements set in the relevant manufacturing and marketing/clinical trial authorizations.

Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by the person responsible for manufacturing, with the involvement of the person/department responsible for quality control when appropriate.

The effects of changes in the production in relation to the quality of the finished product and consistent production (appropriate to the relevant stage of development) should be considered prior to implementation. It is recalled that changes into the manufacturing requirements approved as part of the marketing authorisation must be agreed by the competent authorities and that substantial modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities.

Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated/qualified (*see* Section 10), documented, and shown to be maintained within requirements. For investigational medicinal products, the identification and control strategy of critical parameters should be based on knowledge available at the time.

Any necessary in-process controls and environmental controls should be carried out and recorded.

Checks should be carried out to ensure that premises and equipment are appropriate and in suitable conditions to start production.

9.2. Handling of incoming materials and products

All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and recorded where required. The control strategy must be adequate to the risks.

All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the person/department responsible for quality control.

Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

Intermediate and bulk products[6] purchased as such should be handled on receipt as though they were starting materials.

Sterilisation of articles and materials elsewhere is acceptable provided that there are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitization precautions.

All materials and products should be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation.

Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

At all times during processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

Labels applied to containers, equipment or premises should be clear and unambiguous, preferably in a standard format throughout the facility. It is often helpful, in addition to the wording on the labels, to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.

[6] "Bulk Product" is any product which has completed all processing stages up to, but not including, final packaging.

9.3. Prevention of cross-contamination in production

At every stage of processing, products and materials should be protected from microbial and other contamination. Mix-ups of dedicated (autologous) materials should be prevented.

The majority of ATMPs cannot be terminally sterilized. Therefore, manufacturing of the active substance and the finished product is required to be conducted in appropriate conditions to ensure an aseptic manufacturing. For non-sterile raw or starting materials, additional steps may need to be taken to ensure subsequent aseptic manufacturing (*e.g.* treatment of biopsy with antibiotics, sterile filtration of raw materials, *etc*.).

The risks of cross-contamination should be assessed having regard to the characteristics of the product (*e.g.* biological characteristics of the starting materials, possibility to withstand purification techniques, *etc.*) and manufacturing process (*e.g.* the use of processes that provide extraneous microbial contaminants the opportunity to grow, cleaning processes, *etc.*).

The manufacture of the active substances and finished products should be separated from the manufacturing of other active substances/products, either in place or in time.

Measures to prevent cross-contamination appropriate to the risks identified should be put in place. Measures that can be considered to prevent cross-contamination include, among others:

(i) Dedicated premises and equipment.

(ii) Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness.

(iii) Use of "closed systems" for processing and material/product transfer between equipment.

(iv) Use of single use disposable technologies.

The manufacture of viral vectors and gene therapy medicinal products based on them requires additional precautions. In particular, the manufacturing thereof should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible. Conditions for sample collection, additions and transfers should prevent the release of viral material. Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable.

Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation. For cell-based products, cleaning validation between the manufacturing of different batches should be performed.

The effectiveness of the measures implemented to avoid cross-contamination should be reviewed periodically according to set procedures.

Centrifugation of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.

Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available taking into consideration the organism used in production.

9.4. Other operating principles

The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, *etc.* to bioreactors should be used where possible.

Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

Continuous monitoring of some production processes (*e.g.* in bioreactors) may be necessary, such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

Where chromatography equipment is used, a suitable control strategy for matrices, the housings and associated equipment (adapted to the risks) should be implemented when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilization methods of columns should be defined.

Where irradiated equipment and materials are used, Annex 12 to EudraLex, Volume 4, should be consulted for further guidance.

9.5. Packaging materials

The suitability of primary packaging materials shall be ensured; the specifications provided for in the marketing authorisation or the clinical trial authorisation should be complied with. For commercial production, selection, qualification, approval and maintenance of suppliers of primary packaging materials shall be documented.

ATMPs should be suitably packaged to maintain quality of the product during storage, handling, and shipping.

Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

9.6. Finished products

Finished products should be held in quarantine until their final release under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation.

9.7. Rejected, recovered and returned materials

Where additional donor (human or animal) health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

Rejected materials should be clearly marked as such and stored separately in restricted areas. Starting and raw materials should either be returned to the suppliers or, where appropriate, destroyed. Whatever action is taken, it should be approved and recorded by authorized personnel.

The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the person/department responsible for quality control.

Returned products, which have left the control of the manufacturer, should be destroyed unless without doubt their quality is satisfactory after they have been critically assessed by the person/department responsible for quality control.

10. 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.

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.

Process validation is the documented evidence that the process can consistently produce a result within the specific parameters.

The manufacturing process for investigational ATMPs is not expected to be validated to the extent necessary for commercial ATMPs but it is expected that premises and equipment are qualified (*i.e.* that it is verified that they comply with the specified requirements). Regardless

of the development phase, the aseptic conditions of the manufacturing process have to be validated. Validation of aseptic processing should include a process simulation test using a culture medium (media fill test). Results and conclusions should be recorded.

Manufacturing processes and their control strategies should be under continuous supervision, and they should be improved and optimized as appropriate, especially during the development phase and early phases of clinical trials. It is particularly important to consider steps necessary to reduce process variability and to enhance reproducibility at the different stages of the lifecycle.

When any new manufacturing formula or manufacturing method is adopted, steps should be taken to demonstrate its suitability. Significant changes, which may affect the quality of the product or the reproducibility of the process, should be validated. It is recalled that changes into the manufacturing requirements approved as part of the marketing authorisation must be agreed by the competent authorities and that substantial modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities.

11. 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.

11.1. General principles

Each manufacturing site in the EEA must have at least one Qualified Person ("QP").[7]

Batches of medicinal products should only be released for sale, or supply to the market or for use in clinical trial after certification by a QP. Until a batch is released, it should remain at the site of manufacture or be shipped under quarantine to another authorised site.

Safeguards to ensure that uncertified batches are not released should be in place. These safeguards may be physical (via the use of segregation and labelling) or electronic (via the use of validated computerised systems). When uncertified batches are moved from one authorised site to another the safeguards to prevent premature release should remain.

The requirements for batch release contained in this Section are without prejudice to the specific measures foreseen in the marketing authorisation or clinical trial authorisation. In

[7] Article 48(1) of Directive 2001/83/EC on the Community code relating to medicinal products for human use, (OJ L311, 28.11.2001, p.67). *See* also Article 61(2)(b) of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, (OJ L158, 27.5.2014, p.1).

case of conflict, the provisions in the marketing authorisation or clinical trial authorisation prevail.

11.2. Qualified person

The QP's main responsibility is to verify and certify that each batch produced in the EU has been manufactured and checked in accordance with:

- the requirements of the marketing authorisation or clinical trial authorisation,
- relevant regulations governing the manufacture of medicinal products, including GMPs, and
- relevant product specifications in the destination country (in the case of exports).

In case of imports of investigational ATMPs from third countries, the QP must ensure that the quality of the batch is in accordance with the terms of the clinical trial authorisation and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EU.[8]

In case of imports of commercial ATMPs from third countries, the QP must ensure that the quality of the batch is in accordance with the terms of the marketing authorisation, including by means of a full qualitative and quantitative analysis of the active substances as well as any other necessary checks, including re-testing.[9] For ATMPs, it may be justified to rely on testing performed in the third country, *e.g.* in case of autologous products, as the limited quantities of material available may impede double release testing. In such cases, the testing in the third country should be conducted under conditions equivalent to those applicable in the EU. The re-testing strategy should be in accordance with the terms of the marketing authorisation.

When the QP wishes to rely on testing of samples taken in a third country, transport and storage conditions should be adequate, so as to ensure the samples taken in the third country are still representative of the batch.

In all cases, the conditions of storage and transport should be checked before certifying any batch; these conditions must be in accordance with the terms of the marketing authorisation/clinical trials authorisation.

QPs must have detailed knowledge of the product type and manufacturing steps for which they are taking responsibility.

QPs should have access to:

[8] Article 62 of Regulation (EU) No 536/2014.
[9] Article 51(1)(b) of Directive 2001/83/EC.

- the necessary details of the Marketing Authorisation, or clinical trial authorisation to assess if the relevant requirements have been complied with, and

- relevant data about the entire manufacturing process of the ATMP, including importation activities if any.

Relying on GMP assessments by third parties e.g. audits

In some cases the QP may rely on audits conducted by third parties attesting the general compliance with GMP and the correct functioning of the quality management system of sites involved in the manufacture of the product. In these cases, there should be a clear delimitation of responsibilities and the general requirements in Section 13 apply.

Involvement of more than one QP

The QP who performs certification of the finished product batch may assume full responsibility for all stages of manufacture of the batch, or this responsibility may be shared with other QPs who have confirmed compliance of specific steps in the manufacture and control of a batch.

If a site only undertakes partial manufacturing operations, the QP at that site must (as a minimum) confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible.

Where more than one QP is involved for the assessment of one batch, the division of responsibilities amongst QPs in relation to compliance of the finished batch (including details on the responsibility for assessment of any deviations) should be clearly laid down in writing.

11.3. Batch release

11.3.1. Batch release process

The process of batch release includes the following steps:

(i) Checking that the manufacture and testing of the batch has been done in accordance with applicable requirements, including that:

- all manufacturing steps (including controls and testing) have been done in accordance with the marketing authorisation or clinical trial authorisation,

- the source and specifications of starting materials and packaging materials comply with the terms of the marketing authorisation or clinical trial authorisation, and the provisions in Section 7 and 9.5.,

- the excipients used in the manufacturing of the finished product (including matrixes or devices that are a component of the ATMP) are of suitable quality and that they have been manufactured under adequate conditions,

- for combined ATMPs, the medical device(s) used comply with the essential requirements provided for under the EU rules on medical devices and are validated as being adequate for the use in the combined ATMP,

- where relevant, the microbial safety and TSE status of all materials used in batch manufacture is compliant with the terms of the marketing authorisation or clinical trial authorisation.

- all required in-process controls and checks have been made and appropriate records exists,

- finished product quality control (QC) test data complies with the relevant specifications,

- on-going stability data continues to support certification,

- the impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete,

- all investigations related to the batch being certified has been completed and supports the certification of the batch,

- the self-inspection programme is active,

- appropriate arrangements for storage and transport exist,

- the presence of the safety features referred to in Article 54 of Directive 2001/83/EC have been verified, where appropriate.

It is acknowledged that not all of the elements above will be available in the case of investigational ATMPs. For investigational ATMPs, the assessment of the QP should be based on all existing data and information relevant to the quality of the investigational ATMP.

(ii) Certification of the finished product batch by the QP. The QP must certify that each production batch has been manufactured and checked in accordance with the requirements of the marketing authorisation or clinical trial authorisation, and all other relevant regulatory requirements.

The certification should be recorded by the QP in a register or equivalent document provided for that purpose, which must be kept up to date. The register or equivalent document must remain at the disposal of the competent authority for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the QP, whichever is the longest.

For investigational ATMPs, it is not necessary to create a register but the certification that the batch complies with relevant regulatory requirements must be made available by the sponsor at the request of the relevant competent authority. The certification

must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

Where packaging or labelling is carried out at the sponsor site or in a hospital, health center or clinic, by pharmacists or other persons legally authorised to carry out such activities, the QP is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the QP in this regard.

(iii) Assigning the release status to the batch. This is the step that effectively releases the batch for sale, export, or (in case of an investigational ATMP) use in a clinical study. This step can be done by the QP as an integral part of certification or it can be done afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or a contract.

The notification by a QP to the releasing site that certification has taken place should be formal and unambiguous.

The control reports or another proof of certification for release signed by the QP should be made available for the batches entering another Member State.

It is possible to organise the procedure for batch certification and release in various stages, for example:

- 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.

- Assessment of the final analytical tests and other information available for final certification by the QP.

The delegation of tasks to designated person(s) should be clearly laid down in writing.

11.3.2. Batch release prior to obtaining the results of quality control tests

Due to short shelf-life, some ATMPs may have to be released before completion of all quality control tests. In this case, the exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the quality assurance system is essential (*see* also Section 7).

A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained after the release of the product. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

11.4. Handling of unplanned deviations

As long as the specifications for active substances, excipients and finished products are met, a QP may confirm compliance/certify a batch where an unexpected deviation related to the manufacturing process and/or the analytical control methods has occurred provided that:

- there is an in-depth assessment of the impact of the deviation which supports a conclusion that the occurrence does not have a negative effect on quality, safety or efficacy of the product, and

- the need for inclusion of the affected batch/ batches in the on-going stability programme has been evaluated, where appropriate.

If a significant deviation in the manufacturing process described in the clinical trial dossier has occurred, the event should be notified to the relevant competent authority if the manufacturer wants to release the product.

12. 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.

12.1. General principles

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions which may affect the quality of the product.

The manufacturer of an ATMP should have a person responsible for quality control that is independent from production. The independency of quality control from production is fundamental.

The person responsible for quality control should ensure that the premises and equipment where quality control operations are carried out are appropriate and maintained under suitable conditions and that the personnel working under his/her responsibility is adequately trained. In-process controls may be carried out within the production area provided they do not carry any risk for the product.

The person responsible for quality control supervises all quality control procedures. In particular, it assumes responsibility for the following tasks:

(i) Approval of specifications, sampling instructions, test methods and other quality control procedures.

(ii) Approval of conditions for outsourced testing.

(iii) Control of raw materials, starting materials, packaging materials, intermediate, bulk and finished products (including approval or rejection thereof).

(iv) Supervision of the control of the reference and/or retention samples of materials and products, when applicable.

(v) Ensuring that all necessary testing is carried out and the associated records evaluated.

(vi) Ensuring that the appropriate validations are done.

(vii) Ensuring the correct labelling of containers of materials and products.

(viii) Participation in the investigation of complaints related to the quality of the product.

Appropriate records in connection with the above-referred activities should be kept. Written procedures should be put in place in connection with the activities listed in (iii) to (viii).

Quality control personnel should have access to production areas for sampling and investigation as appropriate. All documents that are needed for the assessment of quality control (*e.g.* procedure description or records from the manufacturing process and testing) should also be accessible.

12.2. Sampling

Samples are generally retained for analytical purposes should the need arise during the shelf life of the batch concerned (reference samples) and for identification purposes (retention samples of a fully packaged unit from a batch of finished product). Samples should be representative of the batch of materials or products from which they are taken.

The sampling plan should be adapted to the specific characteristics of the product. In particular, the following considerations apply:

- Sampling of primary packaging and critical raw materials should be kept. However, for investigational ATMPs sampling of primary packaging is not required.

- Samples of the starting materials, intermediate products, active substance and finished product should be kept where feasible. For biological starting materials, sampling is often not justified due to the nature or the scarcity of the materials.

The sample taking should be done and recorded in accordance with written procedures that describe the method of sampling, including the amount of sample to be taken, precautions to be observed, storage conditions, *etc.*

Containers should bear a label indicating, as a minimum, the content, batch number and date of sampling.

As a general principle, samples of starting materials (other than solvents, gases or water) used in the manufacturing process should be retained for two years after the release of the product. For investigational ATMPs, samples of starting materials should be kept for two years after the completion or formal discontinuation of the clinical trial in which the batch was used, whichever period is longer. However, in all cases, the retention period should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be acceptable. Samples of primary packaging material should be retained for the duration of the shelf-life of the finished product concerned.

Stored samples should be kept under adequate conditions. While the stability of the samples can be modified using specific storage conditions (such as cryopreservation), it should be carefully considered if such specific conditions are suitable for the intended use of the specific sample.

12.3. Testing

Testing is important to ensure that each batch meets the relevant specification. In-process controls testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the product.

Identity testing of starting materials, release testing of the active substance/intermediates/finished products, and stability testing should be performed in accordance with the terms defined in the marketing authorisation/clinical trial authorisation.

Testing methods should be qualified/validated (*see* Section 10) and reference materials should be established for qualification and routine testing if available.

The following records should be kept:

(i) Name of the material or product and, where applicable, dosage form;

(ii) Batch number and, where appropriate, the manufacturer and/or supplier;

(iii) References to the relevant specifications and testing procedures;

(iv) Test results, including observations and calculations, and reference to any certificates of analysis;

(v) Dates of testing;

(vi) Initials of the persons who performed the testing;

(vii) Initials of the persons who verified the testing and the calculations, where appropriate;

(viii) A clear statement of approval or rejection (or other status decision) and the dated signature of the responsible person;

(ix) Reference to the equipment used.

The testing strategy may be affected by the limited availability or short-shelf life of certain materials. In such cases, consideration could be given to the following options:

- Testing of intermediates or in-process controls if the relevance of the results from these tests to the intended material can be demonstrated.

- Replacement of routine batch testing by process validation. While process validation is usually not required for investigational medicinal products, it may be very important when routine in-process or release testing is limited or not possible.

A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence.

A continuous assessment of the effectiveness of the quality assurance system is important. Results of parameters identified as quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined. No trending is however required in connection with an investigational ATMP.

Technical transfer of testing methods

The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.

The transfer protocol should include, among others, the following parameters:

(i) Identification of the testing to be performed and the relevant test method(s) undergoing transfer;

(ii) Identification of the additional training requirements;

(iii) Identification of standards and samples to be tested;

(iv) Identification of any special transport and storage conditions of test items;

(v) The acceptance criteria.

Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.

12.4. Stability monitoring program

After the marketing authorisation is granted, the stability of the medicinal product should be monitored according to a pre-established program designed to detect any stability issue.

The number of batches and frequency of testing should be adequate to allow for trend analysis.

Out of specification or significant atypical trends should be investigated and their possible impact on the batches on the market should be assessed and discussed with the competent authorities as appropriate.

13. 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.

13.1. General principles

Manufacturing activities that are outsourced to a third party should be governed by a written contract that establishes the responsibilities of each party. The role and responsibilities in the event of detection of quality defects should be clearly established in the contract.

13.2. Obligations of the contract giver

Prior to outsourcing any activity, the manufacturer ("contract giver") should assess the suitability of the subcontractor ("contract acceptor") to carry out the subcontracted activities in accordance with the terms of the marketing authorisation/clinical trial authorisation and other applicable regulations, including compliance with GMP.

The contract giver should give to the contract acceptor detailed information on the product, in particular, on those aspects that may impact the quality of the product.

The contract giver must review and assess the records and the analytical results related to the outsourced activities.

13.3. Obligations of the contract acceptor

The contract acceptor should take all necessary measures (*e.g.* adequate premises, equipment, trained personnel, *etc.*) to carry out satisfactorily the subcontracted activities. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

The contract acceptor should not introduce changes in the process, premises, equipment, test methods, specifications or any other element related to the subcontracted activity without the prior approval of the contract giver.

All records related to the outsourced activities as well as reference samples should be kept by, or made available to, the contract giver.

Subcontract to a third party is not permissible without the approval of the contract giver.

The contract acceptor should permit the inspections of the contract giver in connection with the subcontracted activities.

14. 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.

14.1. Quality defects

A system should be put in place to ensure that all quality related complaints, whether received orally or in writing, are recorded and that they are thoroughly investigated.

If a quality defect is discovered or suspected in a batch, consideration should be given to the need of checking other batches (or, as appropriate, other products) in order to determine if they are also affected.

Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems.

The priority during an investigation should be to ensure that appropriate risk-managements measures are taken to ensure patients safety. All decisions and measures adopted should be documented. The authorities should be informed in accordance with the relevant regulations.

The root cause of the quality defect should be investigated. Where the root cause cannot be ascertained, the most probable reasons should be identified.

Appropriate corrective actions should be taken and the effectiveness thereof should be monitored.

Quality defect records should be retained and used to evaluate the possible existence of recurring problems.

14.2. Product recalls

There should be established written procedures for recall of products, including how a recall should be initiated, who should be informed in the event of a recall (including relevant authorities), and how the recalled material should be treated.

15. Environmental control measures for gene therapy products

An emergency plan dealing with accidental release of viable organisms should be in place. The plan should foresee measures/procedures for containment, protection of personnel, cleaning, and decontamination.

16. 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?

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

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

17. 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?