Guidelines on
Good Manufacturing Practice for Advanced Therapy Medicinal Products

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1. Introduction

1.1. Scope

Compliance with good manufacturing practice ("GMP") is mandatory for all medicinal products that have been granted a marketing authorisation. Likewise, the manufacture of investigational medicinal products must be in accordance with GMP. Advanced therapy medicinal products that are administered to patients under Article 3(7) of Directive 2001/83/EC[1] (so called "hospital exemption") must be manufactured under equivalent quality standards.

Article 5 of Regulation (EC) No 1394/2007[2] mandates the Commission to draw up guidelines on good manufacturing practice specific to advanced therapy medicinal products ("ATMPs"). Article 63(1) of Regulation (EU) No 536/2014[3] also empowers the Commission to adopt and publish detailed guidelines on good manufacturing practice applicable to investigational medicinal products.

These Guidelines develop the GMP requirements that should be applied in the manufacturing of ATMPs that have been granted a marketing authorisation and of ATMPs used in a clinical trial setting. These Guidelines do not apply to medicinal products other than ATMPs. In turn, the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC[4] do not apply to ATMPs, unless specific reference thereto is made in these Guidelines.

Throughout these Guidelines, the term "ATMP" should be understood as referring to both advanced therapy medicinal products that have been granted a marketing authorisation and advanced therapy medicinal products that are being tested or used as reference in a clinical trial. When specific provisions are only relevant for advanced therapy medicinal products that have been granted a marketing authorisation, the term "authorised ATMPs" is used. When specific provisions are only relevant for advanced therapy investigational medicinal products, the term "investigational ATMPs" is used.

No provision in these Guidelines (including the risk-based approach) can be regarded as derogation to the terms of the marketing authorisation or clinical trial authorisation. It is noted, however, that non-substantial amendments can be made to the procedures and information stated in the investigational medicinal product dossier without the prior agreement of the competent authorities.[5] Throughout this document, the term "clinical trial

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, 2001 OJ L311/67, as amended.
[2] 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).
[3] 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).
[4] Guidelines published in Volume 4 of EudraLex (https://ec.europa.eu/health/documents/eudralex/vol-4_en).
[5] Regulation (EU) No 536/2014.

authorisation" should be understood as including also non-substantial amendments that have been made to the investigational medicinal product dossier.

Role of marketing authorisation holder / sponsor

For the manufacturer to be able to comply with GMP, cooperation between the manufacturer and the marketing authorisation holder (or, in the case of investigational ATMPs, the manufacturer and the sponsor) is necessary.

The manufacturer should comply with the specifications and instructions provided by the sponsor/marketing authorisation holder. It is the responsibility of the sponsor/marketing authorisation holder to ensure that the specifications/instructions submitted to the manufacturer are in accordance with the terms of the clinical trial authorisation/marketing authorisation. Variations thereto should be notified immediately.

It is important that marketing authorisation holders/sponsors communicate swiftly to the manufacturer any information that is relevant to the manufacturing process, as well as any information that may have an impact on the quality, safety and efficacy of the medicinal product (*e.g.* history of cell-line). The communication of the relevant information should be exhaustive.

In turn, manufacturers should inform the marketing authorisation holder/sponsor of any information that is gathered in the context of the manufacturing activities and that is relevant for the quality, safety or efficacy of the medicinal product.

The obligations of the marketing authorisation/sponsor holder and the manufacturer and vis-à-vis each other should be defined in writing. In the case of investigational products, the agreement between the sponsor and the manufacturer should specifically provide for the sharing of inspection reports and exchange of information on quality issues.

1.2. General principles

Quality plays a major role in the safety and efficacy profile of ATMPs. It is the responsibility of the ATMP manufacturer to ensure that appropriate measures are put in place to safeguard the quality of the product (so-called "pharmaceutical quality system").

Pharmaceutical Quality System

'Pharmaceutical quality system' means the total sum of the arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use.

The size of the company and complexity of the activities should be taken into consideration when designing a pharmaceutical quality system. Senior management should be actively involved to ensure the effectiveness of the pharmaceutical quality system. While some aspects may be company-wide, the effectiveness of the pharmaceutical quality system is normally demonstrated at site level.

Compliance with Good Manufacturing Practice ("GMP") is an essential part of the pharmaceutical quality system. In particular, through the pharmaceutical quality system it should be ensured that:

- the personnel are adequately trained and there is clear allocation of responsibilities;
- the premises and equipment are suitable for the intended use and that there is appropriate maintenance thereof;
- there is an adequate 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 manufacturing process is adequate to ensure consistent production (appropriate to the relevant stage of development), the quality of the product, and the compliance thereof with the relevant specifications;
- there is a quality control system which is operationally independent from production;
- arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory requirements (*i.e.* variations procedure in the case of authorised ATMPs, or authorisation procedure of a substantial modification of a clinical trial in the case of investigational ATMPs), and for the evaluation of changes implemented;
- quality defects and process deviations are identified as soon as possible, the causes investigated, and appropriate corrective and/or preventive measures are taken; and
- adequate systems are implemented to ensure traceability of the ATMPs and of their starting and critical raw materials.

A continuous assessment of the effectiveness of the quality assurance system is important. Results of parameters identified as a 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.

The manufacturer should conduct self-inspections as part of the pharmaceutical quality system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures and/or preventive actions. Records should be maintained of such self-inspections and any corrective actions subsequently taken.

In the case of authorised ATMPs, quality reviews should be conducted to verify the adequacy and consistency of the existing processes, and to highlight any trends and to identify opportunities for product and/or process improvements. The frequency of the reviews should be determined case by case having regard to the specific risks of the product/process and the volume of manufactured products. Quality reviews may be grouped by product type where scientifically justified.

The manufacturer and -when it is a different legal entity- the marketing authorisation holder should evaluate the results of the review and assess whether corrective and/or preventive actions are required.

2. Risk-based approach

2.1. Introduction

ATMPs are complex products and risks may differ according to the type of product, nature/characteristics of the starting materials and level of complexity of the manufacturing process. It is also acknowledged that the finished product may entail some degree of variability due to the use of biological materials and/or complex manipulation steps (*e.g.* cultivation of cells, manipulations that alter the function of the cells, *etc.).* In addition, the manufacture and testing of autologous ATMPs (and allogeneic products in a donor-matched scenario) poses specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material.

ATMPs are at the forefront of scientific innovation and the field is experiencing rapid technological change that also impacts on the manufacturing processes. For instance, new manufacturing models are emerging to address the specific challenges of ATMPs (*e.g.* decentralised manufacturing for autologous products). Additionally, 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.

It follows that, in laying down the GMP requirements applicable to ATMPs, it is necessary to recognise a certain level of flexibility 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. This is particularly important in the case of investigational ATMPs, especially in early phases of clinical trials (phase I and phase I/II), due to the often incomplete knowledge about the product (*e.g.* potency) as well as the evolving nature of the routines (in order to adjust the manufacturing process to the increased knowledge of the product).

While this document describes the standard expectations, alternative approaches may be implemented by manufacturers if it is demonstrated that the alternative approach is capable of meeting the same objective. Any adaptation applied must be compatible with the need to ensure the quality, safety, efficacy and traceability of the product. Additionally, it is stressed that the terms of the marketing/clinical trial authorisation should be complied with.

2.2 Application of the risk-based approach by ATMP manufacturers

The risk-based approach ("RBA") is applicable to all type of ATMPS. It applies in an equal fashion to all type of settings. The quality, safety and efficacy attributes of the ATMPs and compliance with GMP should be ensured for all ATMPs, regardless of whether they are developed in a hospital, academic or industrial setting.

Manufacturers are responsible for the quality of the ATMPs they produce. The risk-based approach permits the manufacturer to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process. While the risk-based approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.

The quality risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells/tissues, the biological characteristics of the vectors *(e.g.* replication competence or reverse transcription) and transgenes, the level and characteristics of the expressed protein (for gene therapy products), the properties of other non-cellular components (raw materials, matrixes), and the manufacturing process. When identifying the control/mitigation measures that are most appropriate in each case, the ATMP manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (*i.e.* the totality of the control and mitigation measures applied) continues to be adequate.

The evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and the accumulated experience. Ultimately, this evaluation is linked to the protection of patients.

The level of effort and documentation should be commensurate with the level of risk. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures *e.g.,* standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable.

The application of a risk-based approach can facilitate compliance but does not obviate the manufacturer's obligation to comply with relevant regulatory requirements. It likewise does not replace appropriate communications with the authorities.

Investigational ATMPs

The application of GMP to investigational ATMPs is intended to protect the clinical trial subjects and it is also important for the reliability of the results of the clinical trial in particular by ensuring consistency of the product used and that changes of the product throughout the development are adequately documented.

The quality and safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowledged that there is a gradual increase in the knowledge of the product and that the level of effort in the design and implementation of the strategy to ensure quality will step up gradually. It follows that, while waivers/additional

adaptations may be possible in the early phases of a clinical trial (phase I and I/II), the manufacturing procedures and control methods are expected to become more detailed and refined during the more advanced phases of the clinical trial.

It is important to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of development. A too immature quality system may compromise the use of the study in the context of a marketing authorisation application (*e.g.* if the product has not been adequately characterised). A weak quality system may also compromise the approval of the clinical trial if the safety of trial subjects is at risk. Accordingly, it is encouraged that the advice of the competent authorities is sought in connection with the implementation of the risk-based approach for investigational ATMPs and, in particular, regarding early phases of clinical trials.

The application of the risk-based approach should be consistent with the terms of the clinical trial authorisation. The description of the manufacturing process and process controls in the clinical trial authorisation application should explain, as appropriate, the quality strategy of the manufacturer when the risk-based approach is applied.

For aspects that are not specifically covered by the clinical trial authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented and to justify that the totality of the measures applied are adequate to ensure the quality of the product. In this regard, it is recalled that alternative approaches to the requirements explained in these Guidelines are only acceptable if they are capable of meeting the same objective.

Authorised ATMPs

For authorised ATMPs, the application of the risk-based approach should be consistent with the terms of the marketing authorisation. When providing the description of the manufacturing process and process controls in the marketing authorisation application (or, as appropriate, in the context of the submission of a variation), account can be taken of the specific characteristics of the product/manufacturing process to justify adaptation/deviation from standard expectations. Thus, the strategy to address specific limitations that may exist in connection with the manufacturing process, including controls of raw materials and starting materials, the manufacturing facilities and equipment, tests and acceptance criteria, process validation, release specifications, or stability data should be agreed as part of the marketing authorisation.

For aspects that are not specifically covered by the marketing authorisation, it is incumbent upon the manufacturer to document the reasons for the approach implemented when the risk-based approach is applied, and to justify that the totality of the measures applied are adequate to ensure the quality of the product. In this regard, it is recalled that alternative approaches to the requirements explained in these Guidelines are only acceptable if they are capable of meeting the same objective.

2.3 Examples of the application of the risk-based approach

This section contains a non-exhaustive list of examples to illustrate some of the possibilities and limitations of the risk-based approach.

2.3.1. RBA in connection with raw materials

The application of the risk-based approach when determining the strategy to ensure the quality of the raw materials is explained in Section 7.2.

The application of the risk-based approach requires that the manufacturer has a good understanding of the role of the raw material in the manufacturing process and, in particular, of the properties of the raw materials that are key to the manufacturing process and final quality of the product.

Additionally, it is important to take into account the level of risk of the raw material due to the intrinsic properties thereof (*e.g.* growth factors *v.* basic media, culture media containing cytokines *v.* basal media without cytokines, raw material from animal origin *v.* autologous plasma, *etc.*), or the use thereof in the manufacturing process (higher risk if the raw material comes into contact with the starting materials).

Finally, it needs to be assessed if the control strategy (*e.g.* qualification of suppliers, performance of suitable functional testing, *etc*.) is sufficient to eliminate the risks or to mitigate them to an acceptable level.

2.3.2. RBA in connection with the testing strategy

It is acknowledged that in some cases it may not be possible to perform the release tests on the active substance or the finished product, for example due to technical reasons (*e.g.* it may not be possible to perform the release tests on the combined components of certain combined products, time restrictions (*i.e.* the product needs to be administered immediately after completion of manufacturing), or when the amount of available product is limited to the clinical dose.

In these cases, an adequate control strategy should be designed. For example, consideration can be given to the following options:

- Testing of key intermediates (instead of the finished product) or in-process controls (instead of batch release testing) if the relevance of the results from these tests to the critical quality attributes of the finished product can be demonstrated.

- Real time testing in case of short shelf-life materials/products.

- Increased reliance on process validation. When the scarcity of materials or the very short shelf-life limits the possibilities for release controls, the limitations should be compensated by a reinforced process validation (*e.g.* additional assays, such as potency testing or proliferation assays may be performed after batch release as supporting data for process validation). This may also be relevant for investigational ATMPs: while process validation is not expected for investigational medicinal

products (*see* Section 10.3), it may be important when routine in-process or release testing is limited or not possible.

As it is not allowed to deviate from the terms of the marketing/clinical trial authorisation, the adaptation of the release testing strategy should be agreed by the competent authorities in the marketing authorisation/clinical trials authorisation application.

The following examples may also be considered:

- The application of the sterility test to the finished product in accordance with the European Pharmacopoeia (Ph. Eur. 2.6.1) may not always be possible due to the scarcity of materials available, or it may not be possible to wait for the result of the test before the product is released due to short shelf-life. In these cases, the strategy regarding sterility assurance may need to be adapted. For example, the use of alternative methods for preliminary results, combined with sterility testing of media or intermediate product at subsequent (relevant) time points could be considered.

  Sole reliance on alternative microbiological methods according to Ph. Eur. 2.6.27 (Microbiological control of cellular products) may be acceptable when this is justified having regard to the specific characteristics of the product and the related risks, and provided that the suitability of the method for the specific product has been validated.

  If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including informing the treating physician (*see* Section 11.3.2).

- As cells in suspension are not clear solutions, it is acceptable to replace the particulate matter test by an appearance test (*e.g.* colour), provided that alternative measures are put in place, such as controls of particles from materials (*e.g.* filtration of raw material solutions) and equipment used during manufacturing, or the verification of the ability of the manufacturing process to produce low particle products with simulated samples (without cells).

- It may be justified to waive the on-going stability program for products with shorter shelf-life.

2.3.3. Additional considerations specifically relevant for ATMPs that are not subject to substantial manipulation

Manufacturing processes of ATMPs not involving substantial manipulation of the cells/tissues are typically associated with lower risks than the manufacturing of ATMPs involving complex substantial manipulations. However, it cannot be inferred that processes that are not qualified as "substantial manipulation" are risk-free, notably if the processing of the cells entails long exposure of the cells/tissues to the environment. Accordingly, an analysis of the risks of the specific manufacturing process should be performed in order to identify the measures that are necessary to ensure the quality of the product.

With a view to reduce administrative burden, in the application of the GMP requirements to ATMPs the manufacturing process of which does not involve substantial manipulation, account may be taken of equivalent standards that are applied by ATMP manufacturers in compliance with other legislative frameworks. For instance, premises and equipment that have been duly validated to process cells/tissues for transplantation purposes in accordance with standards that can be deemed comparable to those laid down in these Guidelines need not being validated again (for the same type of manufacturing operation). However, premises/equipment used to process cells/tissues under the same surgical procedure derogation[6] or for research purposes should be qualified in accordance with these Guidelines.

However, there are certain elements of GMP that are intended to ensure the quality, safety and efficacy of the ATMPs which are not specifically addressed under other legislative frameworks and which, therefore, should follow the requirements in these Guidelines, also when the manufacturing process does not involve substantial manipulation. In particular, the requirements on product characterisation (through the setting of adequate specifications), process validation (the expectations for investigational ATMPs are described in Section 10.3), quality controls (in accordance with the terms of the marketing/clinical trial authorisation), and QP certification should be complied with.

2.3.4. Additional considerations specifically relevant for investigational ATMPs

While additional adaptations in the application of GMP may be justified in the case of investigational ATMPs, it is stressed that the quality, safety and traceability of the product should be ensured also in a clinical trial setting.

The following are examples of additional possible adaptations that may be acceptable in the case of investigational ATMPs:

- For first-in-man clinical trials, production in an open system may be performed in a critical clean area of grade A with a background clean area of grade C if appropriate controls of microbiological contamination, separation of processing procedures, and validated cleaning and disinfection procedures are put in place. A risk-analysis study should be conducted and it should be demonstrated that the implemented control measures are adequate to ensure aseptic manufacturing (*e.g.* every unit manufactured is subject to sterility testing and the results of the test are available prior to administration of the product to the patient).

- In early phases of clinical research (clinical trial phases I and I/II) when the manufacturing activity is very low, calibration, maintenance activities, inspection or checking of facilities and equipment should be performed at appropriate intervals, which may be based on a risk-analysis. The suitability for use of all equipment should be verified before it is used.

[6] Article 2(2) of Directive 2004/23 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 L102, 7.04.2004,p.48).

- The level of formality and detail for the documentation can be adapted to the stage of development.

- During early phases of clinical development (clinical trial phases I and I/II) specifications can be based on wider acceptance criteria taking due account of the current knowledge of the risks and as approved by the competent authority that authorises the clinical trial.

- Possible adaptations regarding qualification of premises and equipment, cleaning validation, process validation, and validation of analytical methods are described in Section 10.

3. Personnel

3.1. General principles

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 their tasks and responsibilities, including knowledge of the product appropriate to the assigned tasks.

3.2. Training

All personnel should receive training on the principles of GMP that affect them and receive initial and periodic training relevant to their tasks.

There should be appropriate (and periodic) training in the requirements specific to the manufacturing, testing, and traceability of the product.

Personnel working in clean areas should be given specific training on aseptic manufacturing, including the basic aspects of microbiology.

Prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test (*see* Section 9.5.2). Training in the gowning requirements set out in section 3.3 is also required. The competence of personnel working in grade A/B areas to comply with the gowning requirements should be reassessed at least annually.

Microbial monitoring of personnel working in A/B areas should be performed after critical operations and when leaving the A/B area. A system of disqualification of personnel should be established based on the results of the monitoring program, as well as other parameters that may be relevant. Once disqualified, retraining/requalification is required before the operator can be involved in aseptic operations. It is advised that the retraining/requalification includes participation in a successful process simulation test.

In addition, there should be appropriate training to prevent the transfer of communicable diseases from biological raw and starting materials to the operators and vice versa. Personnel

handling genetically modified organisms ("GMOs") require additional training to prevent cross-contamination risks and potential environmental impacts.

Cleaning and maintenance personnel should also receive training relevant to the tasks performed, in particular on measures to avoid risks to the product, to the environment, and health risks.

Training can be provided in-house. The effectiveness of training should be periodically assessed. Records of training should be kept.

3.3. Hygiene

High standards of personal hygiene and cleanliness are essential. Hygiene programs should be established.

Eating, drinking, chewing or smoking, as well as the storage of food or personal medication should be prohibited in the production and storage area.

Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

Every person entering the manufacturing areas should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective garments appropriate to the operations to be carried out (*e.g.* head, face, hand and/or arm coverings) should be worn when necessary.

The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the operator and the product from the risk of contamination.

The description of clothing required for clean areas is as follows:

- Grade D: Hair and, where relevant, beard and moustache should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

- Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

- Grade A/B: Sterile headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a sterile face mask and sterile eye coverings should be worn to prevent the shedding of droplets and particles. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves

into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean (sterilised) protective garments (including face masks and eye coverings) should be provided every time there is an entry into the clean area; the need to exit and re-enter the clean area for a different manufacturing step/different batch should be determined by the risk of the activity. Gloves should be regularly disinfected during operations. Upon exit from a clean area there should be a visual check of the integrity of the garment.

Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. When working in a contained area, protective clothing should be discarded before leaving the contained area.

Wristwatches, make-up and jewellery should not be worn in clean areas.

Where required to minimise the risk for cross-contamination, restrictions on the movement of all personnel should be applied. In general, personnel (or any other person) should not pass directly from areas where there is exposure to live micro-organisms, GMOs, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, appropriate control measures (having regard to the risks) should be applied. When a person moves from one clean room to another clean room (higher to lower grade, or lower to higher grade) appropriate disinfection measures should be applied. The garment requirements required for the relevant grade should be respected.

Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum. Excessive shedding of particles and organisms due to over-vigorous activity should be avoided.

Only the minimum number of personnel should be present in clean areas. Inspections and controls should be conducted outside the clean areas as far as possible.

Steps should be taken to ensure that health conditions of the personnel that may be relevant to the quality of the ATMP are declared and that no person affected by an infectious disease which could adversely affect the quality of the product, or having open lesions on the exposed surface of the body, is involved in the manufacture of ATMPs.

Health monitoring of staff should be proportional to the risks. Where necessary having regard to the specific risks of the product, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated. Other measures may need to be put in place to protect the personnel according to the known risks of the product and of the materials used in the manufacture thereof.

3.4. Key personnel

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. In case of ATMPs containing or consisting of GMOs, the person responsible for biosafety should also be appointed by senior management.

The roles and responsibilities of key personnel should be clearly defined and communicated within the organisation.

As a minimum, the person responsible for production should take responsibility for ensuring that manufacturing is done in accordance with the relevant specifications/instructions, for the qualification and maintenance of the premises and equipment used in manufacturing operations, and to ensure that appropriate validations are done. The responsibilities of the person responsible for quality control are detailed in Section 12(1) and the responsibilities of the QP are explained in Section 11(2).

Additionally, depending on the size and organisational structure of the company, a separate unit responsible for quality assurance may be established. In this case, the responsibilities of the person responsible for production and the person responsible for quality control are shared with the person responsible for quality assurance.

The person responsible for production, the person responsible for quality control, and -where relevant- the person responsible for quality assurance, share some responsibilities regarding the design and implementation of the pharmaceutical quality system and in particular concerning training, documentation obligations, process validation, validation of the transport conditions and of the reconstitution process (where applicable), control of the manufacturing environment, control of outsourced activities, and quality investigations.

While the duties of key personnel may be delegated to persons with appropriate qualification, there should be no gaps or unexplained overlaps in the responsibilities of key personnel.

Responsibility for production and for quality control cannot be assumed by the same person. In small organisations, where teams are multi-skilled and trained in both quality control and production activities, it is acceptable that the same person is responsible for both roles (production and quality control) with respect to different batches. For any given batch, the responsibility for production and quality control of the batch must be vested on two different persons. Accordingly, it becomes particularly important that the independency of the quality control activities from the production activities for the same batch is clearly established through appropriate written procedures.

The same person can perform the role of person responsible for quality control and QP. It is also possible for the QP to be responsible for production, provided that the same person is not involved in the production and certification of the same batch.

4. Premises

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 extraneous contamination, cross-contamination, the risk of errors and, in general, any adverse effect on the quality of products.

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 for the activities performed and should not adversely affect the ATMPs or the functioning of equipment.

(d) Appropriate measures to monitor key environmental parameters should be applied.

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

(f) Steps should be taken 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. When such passage is unavoidable, appropriate control measures should be applied.

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

For production of ATMPs, the premises should be qualified (*see* Section 10.1).

4.2. Multi-product facility

Manufacture of ATMPs in a multi-product facility is acceptable when appropriate risk-mitigation measures commensurate with the risks are implemented to prevent mix-ups and cross-contamination. Further explanations can be found in Section 9.4.

If the manufacturing site produces medicinal products other than ATMPs, based on a risk assessment, the manufacture of ATMPs may need to take place in a dedicated area of the facility.

Segregated production areas should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. Where there are no separate production suites, a thorough cleaning and decontamination procedure of validated effectiveness should take place before any subsequent manufacturing in the same area can occur (segregation in time).

Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (*e.g.* oncolytic viruses): these activities should take place in a segregated area.

<u>Concurrent manufacturing of different batches/products</u>

Manufacturing activities concerning different starting materials and/or finished products should be separated, either in place or in time.

4.2.1. Separation in place:

Concurrent production of two different ATMPs/batches in the same area is not acceptable. However, closed and contained systems may be used to separate activities as follows:

(i) The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials, including separated expulsion of the exhausted air from the isolators and regular integrity checks of the isolator.

When two isolators are used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility (*i.e.* no recirculation). In other cases, air filtration may be acceptable. In addition, in case of concurrent production of viral vectors, it is necessary to provide for closed, separate and unidirectional waste handling.

(ii) The possibility of using more than one biosafety cabinet in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities (*e.g.* strict material and personal flows defined, no crossing lines in the use of equipment in the same room *etc*.). It is stressed that the simultaneous use of more than one biosafety cabinet entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid risks to the quality of the product and mix-ups.

(iii) It is acceptable to conduct a manufacturing activity in a clean room which hosts an incubator which is used for a different batch/product if there is separated expulsion of exhausted air from the incubator. Particular attention should be paid to prevent mix-ups.

(iv) The simultaneous incubation/storage of different batches within the same incubator is only acceptable if they are physically separated (*e.g.* distinct cell cultures in closed vessels). When simultaneous incubation/storage of different batches takes place as described above, the manufacturer should evaluate the possible risks and implement appropriate measures to avoid mix-ups of materials.

However, the simultaneous incubation/storage of replication competent vectors/products based on them, or infected material/products based on them with other materials/products is not acceptable.

(v) Given their lower risk profile, concurrent production of non-viral vectors in separate laminar flow hoods placed in the same room may be acceptable if appropriate measures are implemented to avoid mix-ups.

4.2.2. Separation in time:

The whole manufacturing facility or a self-contained production area may be dedicated to the manufacturing of a specific product on a campaign basis followed by a cleaning process of validated effectiveness (*see* Section 10.2).

4.3. Production areas

4.3.1. Design and construction

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 of the equipment and materials should be adequate to minimise the risk of confusion between different 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 lay out of the premises should permit the separation of flows of non-sterile and used materials and equipment from those sterilised. Where this is not possible, the handling of non-sterile and used materials/equipment should be separated in time and appropriate cleaning measures should be applied.

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

Air handling units should be designed, constructed, and maintained to prevent the risk of cross-contamination between different areas in the manufacturing site 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.

4.3.2. Aseptic environment

Premises should be suitable for the intended operations and they should be adequately controlled to ensure an aseptic environment. The measures implemented to ensure an aseptic environment should be adequate having regard to all the specific risks of the product and the manufacturing process. Special attention should be paid when there is no terminal sterilisation of the finished product.

<u>Clean areas</u>

A critical clean area is an area where the product is exposed to environmental conditions and the design thereof should therefore be designed to ensure aseptic conditions. The air in the immediate vicinity of the critical clean area should be adequately controlled also (background clean area). Clean areas should be supplied with air which has passed through filters of an appropriate efficiency. The appropriate level of air classification should be determined having regard to the specific risks taking into account the nature of the product and the manufacturing process, in particular whether processing takes place in an open or closed system (*see* Section 9.5.1).

The classification of clean rooms/clean air devices should be done according to ISO 14644-1. For qualification, the airborne particles equal to or greater than 0.5 µm should be measured. This measurement should be performed at rest and in operation. The maximum permitted airborne particle concentration for each grade is as follows:

	Maximum permitted number of particles equal or greater than 0.5 µm		
	At rest (per $m^{3)}$	In operation (per $m^{3)}$	ISO classification (At rest/in operation)
Grade			
A	3 520	3 520	5/5
B	3 520	352 000	5/7
C	352 000	3 520 000	7/8
D	3 520 000	Not defined	8

As part of the qualification of clean rooms, the microbial load of the clean room in operation should be measured. The limits for microbial contamination for each grade are as follows (recommended values):

Grade	Air sample cfu/m3	Settle plates (diameter 90mm) cfu/4 hours*	Contact plates (diameter 55 mm) cfu/plate
A**	<1	<1	<1
B	10	5	5
C	100	50	25
D	200	100	50

*Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours.

** It should be noted that for grade A the expected result should be 0 cfu recovered; any recovery of 1 cfu or greater should result in an investigation.

The presence of containers and/or materials liable to generate particles should be minimised in the clean areas.

Appropriate cleaning/sanitation of clean areas is essential, including the removal of residual cleaning agents/disinfectants. Fumigation may be useful to reduce microbiological contamination in inaccessible places. Where disinfectants are used, it is advisable that more than one type is used to avoid the development of resistant strains and to achieve a broader

range of bio-decontamination activity. Disinfectants, detergents and cleaning materials used in clean areas of grades A and B should be sterile.

Clean/contained areas should be accessed through an air lock with interlocked doors or by appropriate procedural controls to ensure that both doors are not opened simultaneously. The final stage of the air lock should, in the at-rest state, be the same grade as the area into which it leads.

Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and to minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

4.3.3. Environmental monitoring

Environmental monitoring programs are an important tool by which the effectiveness of contamination control measures can be assessed and specific threats to the purity of the products be identified. The environmental monitoring program should include the following parameters: non-viable/viable contamination, air pressure differentials, and -where appropriate control is required for the process- temperature and relative humidity.

The monitoring locations should be determined having regard to the risks (*e.g.* at locations posing the highest risk of contamination) and the results obtained during the qualification of the premises.

The number of samples, volume, frequency of monitoring, alert and action limits should be appropriate taking into account the risks and the overall control strategy for the site. Sampling methods should not pose a risk of contamination to the manufacturing operations.

<u>Non-viable particulate monitoring</u>

Airborne particle monitoring systems should be established to obtain data for assessing potential contamination risks and to ensure an aseptic environment in the clean room. Environmental monitoring is also expected for isolators and biosafety cabinets.

The degree of environmental control of non-viable particulate and the selection of the monitoring system should be adapted to the specific risks of the product and of the manufacturing process (*e.g.* live organisms). The frequency, sampling volume or duration, alert limits and corrective actions should be established case by case having regard to the risks. It is not necessary for the sample volume to be the same as that used for qualification of the clean room.

Appropriate alert and actions limits should be defined. With a view to identify potential changes that may be detrimental to the process, the alert limits for grades B to D should be lower than those specified as action limits and should be based on the area performance.

The monitoring system should ensure that when alert limits are exceeded, the event is rapidly identified (*e.g.* alarm settings). If action limits are exceeded, appropriate corrective actions should be taken. These should be documented.

The recommended action limits are as follows:

Grade	**Recommended maximum limits for particles ≧ 0.5 µm/m^3**		**Recommended maximum limits for particles ≧ 5 µm/m^3**	
	in operation	at rest	in operation	at rest
A	3 520	3 520	20*	20*
B	352 000	3 520	2 900	29
C	3 520 000	352 000	29 000	2 900
D	Set a limit based on the risk assessment	3 520 000	Set a limit based on the risk assessment	29 000

* Due to limitations of monitoring equipment a value of 20 has been retained. Frequent sustained recoveries below that value should also trigger an investigation.

For grade A areas, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where duly justified (*e.g.* contaminants in the process that would damage the particle counter or when this would present a hazard, *e.g.* live pathogenic organisms). In such cases, monitoring during equipment set-up operations should take place (*i.e.* prior to exposure of the product to the hazard). Monitoring should also be performed during simulated operations.

For grade B areas, there should be particle monitoring during critical operations, albeit the monitoring does not need to cover the entire duration of the critical processing. The grade B area should be monitored at an appropriate frequency and with suitable sample size to permit that changes in levels of contamination are identified.

The monitoring strategy regarding grades C and D should be set having regard to the risks and in particular the nature of the operations conducted.

When there is no critical operations on-going (*i.e.* at rest), sampling at appropriate intervals should be conducted. While at rest, the HVAC system should not be interrupted, as this may trigger the need for re-qualification. In the event of an interruption, a risk assessment should be conducted to determine any actions that may be required taking account of the activities performed in the affected areas *(e.g.* additional monitoring).

While not required for qualification purposes, the monitoring of the ≥5.0 µm particle concentration in grade A and B areas is an important diagnostic tool for early detection of failures. While the occasional indication of ≥5.0 µm particle counts may be false counts, consecutive or regular counting of low levels is an indicator of a possible contamination and it should be investigated. Such events may, for example, be indicative of early failure of the

HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

Viable particle monitoring

Checks to detect the presence of specific microorganisms in the clean room (*e.g.* yeast, moulds, *etc.*) should be performed as appropriate. Viable particle monitoring is also expected for isolators and biosafety cabinets.

Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (*e.g.* swabs and contact plates). Rapid microbial monitoring methods should be considered and may be adopted after validation of the premises.

Continuous monitoring is required during critical operations where the product is exposed to the environment. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring may also be required outside production operations depending on the risks.

The following recommended maximum limits for microbiological monitoring of clean areas apply:

Grade	Air sample cfu/m3	Settle plates (diameter 90mm) cfu/4 hours*	Contact plates (diameter 55 mm) cfu/plate	glove print 5fingers cfu/glove
A**	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

*Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours.

** It should be noted that for grade A the expected result should be 0 cfu recovered; any recovery of 1 cfu or greater should result in an investigation.

Appropriate alert and actions limits should be defined. With a view to identify potential changes that may be detrimental to the process, the alert limits for grades B to D should be lower than those specified as action limits and should be based on the area performance. If action limits are exceeded, appropriate corrective actions should be taken. These should be documented.

If microorganisms are detected in a grade A area, they should be identified to species level and the impact thereof on product quality and on the suitability of the premises for the intended operations should be assessed.

Air pressure

An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is fundamental for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. These pressure cascades should be clearly defined and continuously monitored with appropriate methods (*e.g.* alarm settings). Adjacent rooms of different grades should have a pressure differential of 10-15 Pa (guidance values).

However, negative pressure in specific areas may be required in for containment reasons (*e.g.* when replication competent vectors or pathogenic bacteria are used). In such cases, the negative pressure areas should be surrounded by a positive pressure clean area of appropriate grade.

4.3.4. Drains

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. Manufacturers are reminded that, for risks relating to biohazard waste, local regulations should be followed.

Clean areas of grade A and B should not have sinks or drains installed.

4.4. Storage areas

Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and raw materials, 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 should be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

Separated areas should be provided for the storage of recalled and returned materials/products, unless control of these materials/products is ensured through electronic means. Rejected materials/products should be stored in restricted areas (*e.g.* locked).

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

4.5. Quality control areas

Quality 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 during testing. There should be adequate suitable storage space for samples and records.

Quality control laboratories should normally be separated from production areas. However, in-process controls may be carried out within the production area provided that they do not carry any risk for the products. Further details are available in Section 12.1.

4.6. Ancillary areas

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

Premises where laboratory animals are kept should be isolated from production, storage and quality control areas with separate entrance and air handling facilities. Appropriate restrictions of movement of personnel and materials should be put in place.

5. Equipment

5.1. General principles

Equipment used in production or control operations should be suitable for its intended purpose and it should not present any hazard to the product. Parts of production equipment that come into contact with the product should not have unwanted reactive, additive, adsorptive or absorptive properties that may affect the quality of the product. In addition, parts of the equipment that come into contact with cells/tissues should be sterile.

Major equipment (*e.g.* reactors, storage containers) and permanently installed processing lines should be appropriately identified to prevent mix-ups.

The integrity of the equipment´s components should be verified as appropriate having regard to the specific risk of the product and the intended manufacturing process (*e.g.* ensuring structural integrity during freeze and thawing).

The location and installation of the equipment should be adequate to minimise risks of errors or contamination. Connections that are to be made in aseptic conditions should be performed in a critical clean area of grade A with a background clean area of grade B, unless there is subsequent sterilisation by steam-in-place or the connection is made by means of a validated sterile system (*e.g.* sterile tube welders, aseptic connection with a sterile septum).

Balances and measurement equipment should be of appropriate range and precision to ensure the accuracy of weighing operations.

Qualification of relevant equipment should be done in accordance with the principles in Section 10.1.

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

5.2. Maintenance, cleaning, repair

Equipment should be adequately maintained:

- Equipment should be calibrated, inspected or checked (as appropriate) at defined intervals to ensure adequate performance. In the case of computerised systems, the checks should include an evaluation of the ability of the system to ensure data integrity. Appropriate records of those checks should be maintained.

- Air vent filters should be adequately qualified and maintained and should be changed at appropriate intervals (to be set according to the criticality of the filter). Qualification can be done by the manufacturer, or by the supplier/manufacturer of the filter. When replaced, the filter should be subject to an integrity test.

Adequate cleaning and storage of the equipment is essential in order to avoid the risk of contamination for the products. Whenever possible, single-use cleaning materials should be used. The cleaning/decontamination procedures applied to multi-use equipment coming into contact with the product should be validated as explained in Section 10.2.

Repair and maintenance operations should not present any hazard to the quality of the products. As far as possible, maintenance and repair operations should be done outside the clean area. When repair or cleaning operations occur in a clean area, production should not be restarted until it has been verified that the area has been adequately cleaned and that the required environmental status has been re-established.

Where required to minimise the risk of cross-contamination, restrictions on the movement of equipment should be applied. In general, equipment should not be moved from high risk areas to other areas, or between high risk areas (*e.g.* equipment used for the handling of cells from infected donors or the handling of oncolytic viruses). When this happens, appropriate measures need to be applied to avoid the risk of cross-contamination. The qualification status of the equipment moved should also be reconsidered.

6. Documentation

6.1. General principles

Good documentation is an essential part of the quality system and is a 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 the medicinal products. Records required to ensure traceability should also be kept.

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

Documentation may exist in a variety of forms, including paper-based, electronic, photographic media or video recording.

Irrespective of the form in which data is kept, suitable controls should be implemented to ensure data integrity, including:

- Implementation of measures to protect data against accidental loss or damage, *e.g.* by methods such as duplication or back-up and transfer to another storage system.

- Implementation of measures to protect the data against tampering or unauthorised manipulation. Physical and/or logical controls should be in place to limit access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include *e.g.* the use of keys, pass cards, personal codes with passwords, biometrics, or restricted access to computer equipment and data storage areas. The extent of security controls depends on the criticality of the computerised system

- Implementation of measures to ensure the accuracy, completeness, availability and legibility of documents throughout the retention period.

The content of documents should be unambiguous.

6.2. Specifications and Instructions

The specifications for the materials and the finished product and the manufacturing instructions are intended to ensure compliance with the terms of the marketing authorisation/clinical trial authorisation, product consistency (appropriate to the relevant stage of development), and the required level of quality. Therefore, it is important that specifications and instructions are documented appropriately and that they are clear and detailed enough.

Documents containing specifications and instructions (including changes thereto) should be approved, signed and dated by authorised persons and the date of entry into operation should be defined. Steps should be taken to ensure that only the current version of a document is used.

Specifications and instructions should be periodically re-assessed during development and post-authorisation and be updated as necessary. Each new version should take into account the latest data, current technology used, as well as the terms of the marketing authorisation/clinical trial authorisation. It should also allow traceability to the previous document.

Rationales for changes should be recorded and the consequences of a change on product quality, safety or efficacy and, where applicable, on any on-going non-clinical study or clinical trials should be investigated and documented. It is noted that changes to the manufacturing requirements approved as part of the marketing authorisation must be submitted to the competent authorities (variation procedure),[7] and that substantial

[7]Commission Regulation (EC) No 1234/2008 of 24 of November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L334, 12.12.2008, p.7), as amended.

modifications in the manufacturing process of an investigational ATMP also require approval by the competent authorities.[8]

As a minimum, the following should be documented:

(i) Specifications for raw materials, including:
- Description of the raw materials, including reference to designated name and any other information required to avoid risks of error (*e.g.* use of internal codes). In addition, for raw materials of biological origin, the identification of the species and anatomical environment from which materials originate should also be described.
- For critical raw materials (*e.g.* sera, growth factors, enzymes (*e.g.* trypsin), cytokines), quality requirements to ensure suitability for intended use, as well as acceptance criteria (*see* Section 7.2). Quality requirements agreed with suppliers should be kept.
- Instructions for sampling and testing, as appropriate (*see* Section 7.2, 12.2 and 12.3).
- Storage conditions and maximum period of storage.
- Transport conditions and precautions.

(ii) Specifications for starting materials, including:
- Description of the starting materials, including any relevant information required to avoid risks of error (*e.g.* use of internal codes). For starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells/tissues/virus originate (or, as appropriate, the identification of the cell-line, master cell bank, seed lot) should also be described.
- Quality requirements to ensure suitability for intended use, as well as acceptance criteria (*see* Section 7.3). Contracts and quality requirements agreed with the suppliers should be kept.
- Instructions for sampling and testing (*see* Sections 7.3, 12.2 and 12.3).
- Storage conditions and maximum period of storage.
- Transport conditions and precautions.

(iii) Specifications for intermediate and bulk products should be available where applicable, including release criteria and maximum period of storage.

(iv) Specifications for primary packaging materials, including release criteria.

(v) Where applicable, specifications for other materials that are used in the manufacturing process and that can have a critical impact on quality (*e.g.* medical devices used in a combined ATMP, materials and consumables that have an inherent biological activity through which they can impact cells, such as mAb coated dishes or beads).

(vi) Batch definition. Products generated from different starting materials should be considered a distinct batch.

(vii) Manufacturing instructions, including description of principal equipment to be used.

[8] The definition of substantial modification is provided for under Article 2.2(13) of the Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

(viii) Specifications for finished products, in particular:

- Name/identification of the product.
- Description of the pharmaceutical form.
- Instructions for sampling and testing (*see* Sections 12.2 and 12.3).
- Qualitative and quantitative requirements with acceptance limits.
- Storage and transport conditions and precautions. Where applicable, particular attention should be paid to the requirements at cryopreservation stage (*e.g.* rate of temperature change during freezing or thawing) to ensure the quality of the product.
- The shelf-life.

(ix) Where applicable, the control strategy to address cases when test results for starting materials, intermediates and/or finished product are not available prior to product release (*see* Section 11.3.2).

(x) Packaging instructions for each product. Particular attention should be paid to ensuring the traceability of the product. It is noted that, for authorised ATMPs, the donation identification code received from the tissue establishment/blood establishment should be included in the outer packaging or, where there is no outer packaging, on the immediate packaging. Other labelling requirements are laid down in Article 11 of Regulation (EC) No 1394/2007.

Investigational ATMPs: the Product Specification File

In the case of investigational ATMPs, the level of detail of the specifications and instructions should be adapted to the type of product and to the stage of development. Given the evolution/refinement of the manufacturing process and quality controls that is typical of investigational products, it is important that the level of documentation is sufficient to enable the identification of the specific characteristics of each batch. It is also noted that a deficient characterization of the product may hinder the acceptability of the results of the clinical trial for the purposes of obtaining a marketing authorisation.

In addition to the specifications and instructions, the Product Specification File should contain appropriate documentation of the system used to ensure the blinding, while allowing for identification of the product when necessary. The effectiveness of the blinding procedures should be verified.

A copy of the manufacturing order and a copy of the approved label should also be kept as part of the Product Specification File.

The information contained in the Product Specification File should form the basis for assessment of the suitability for certification and release of a particular batch by the QP and should therefore be accessible to him/her.

6.3. Records/reports

Records provide evidence that the relevant specifications/instructions have been complied with. Records should be made or completed at the time each action is taken. Any change to a record should be approved, signed and dated by authorised persons.

The level of documentation will vary depending on the product and stage of development. The records should enable the entire history of a batch to be traced. Additionally, the records/reports 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 internal code if appropriate;
- supplier's name and manufacturer's name;
- supplier's batch or reference number;
- total quantity received;
- date of receipt;
- unique receipt 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;
- quantities and batch number of critical raw materials;
- where applicable, quantities and batch number of other materials that are used in the manufacturing process and that can have a critical impact on quality, (*e.g.* medical devices used in a combined ATMP, materials and consumables that have an inherent biological activity through which they can impact cells, such as mAb coated dishes or beads);
- confirmation that line-clearance has been performed prior to starting manufacturing operations;
- identification (*e.g.* by means of initials or another suitable system) 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;
- identification of clean room and major equipment used;
- the product yield obtained at relevant stages of manufacture; and

- notes on special problems including details, with signed authorisation for any deviation from the manufacturing instructions.

(iii) Results of release testing.

(iv) Environmental monitoring records.

(v) On-going stability program in accordance with Section 12.4 (for authorised ATMPs).

Any deviations should be recorded and investigated, and appropriate corrective measures should be taken.

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 of premises and equipment.

(ii) Validation of manufacturing process (the expectations for investigational ATMPs are described in Section 10.3).

(iii) Validation of relevant analytical methods.

(iv) Maintenance and calibration of equipment.

(v) Cleaning procedures.

(vi) Environmental monitoring.

(vii) Investigations into deviations and non-conformances.

(viii) Outcome of self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

(ix) Procedures for handling of quality complaints and recall of products.

Logbooks should be kept for equipment used for critical manufacturing and testing operations.

The documentation of the above policies and procedures should be adjusted to the stage of development. The documentation for phase I and I/II clinical trials can be more limited but it is expected that it becomes more comprehensive in later phases of development.

A site master file should be prepared for every site involved in manufacturing of authorised ATMPs. The site master file should provide a high level description of the premises, activities conducted at the site and of the quality system implemented.[9]

6.5. Retention of documents

Without prejudice to Section 6.6, batch documentation (*i.e.* documents in the batch processing record, results of release testing, as well as -where applicable- any data on product related deviations) should be kept for one year after expiry of the batch to which it relates or at least

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

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.

It is acceptable that some of the data pertaining to the batch documentation is kept in a separate file, provided that they are readily available and are unequivocally linked to the relevant batch.

Critical documentation, including raw data (for example relating to validation or stability) that 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.

6.6. Traceability data

A system that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, to the delivery of the finished product to the recipient should be created. Such system, which can be manual or electronic, should be established since the beginning of the manufacture of batches for clinical use.

In accordance with Article 15 of Regulation 1394/2007, traceability information should also cover raw materials and all substances coming into contact with the cells or tissues. This Section describes the type and amount of data that must be generated and kept by manufacturers of ATMPs.

The manufacturer should ensure that the following data is retained for a minimum of 30 years after the expiry date of the product, unless a longer period is provided for in the marketing authorisation:

(i) Donation identification code received from the tissue establishment/blood establishment. For cells and tissues that are not covered by Directive 2004/23/EC[10] or Directive 2002/98/EC[11], such as *e.g.* cell-lines or cell-banks established outside the EU, information permitting the identification of the donor should be kept.

(ii) Internal code (or other identification system) that is generated by the manufacturer to unequivocally identify the tissues/cells used as starting materials throughout the entire manufacturing process up to the point of batch release. The manufacturer must ensure that the link between the internal code and the donation identification code can always be established. For starting materials not covered by Directive 2004/23/EC or

[10] Directive 2004/23 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 L102, 7.04.2004,p.48).

[11] 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).

Directive 2002/98/EC, it should be ensured that a link between the internal code and the donor identification can always be established.

(iii) Identification (including batch number) of critical raw materials and other substances that come into contact with the cells or tissues used as starting materials that may have a significant impact on the safety of the finished ATMP (*e.g.* reagents of biological origin, scaffolds, matrixes). For biological materials, the identification of the supplier, species and anatomical environment from which materials originate should also be described.

(iv) Where applicable, identification (including batch number) of all other active substances that are contained in the ATMPs.

When xenogeneic cells are used as starting materials for ATMPs, information permitting the identification of the donor animal should be kept for 30 years.

Traceability data should be kept as auditable documents. It is acceptable that it is kept outside the batch processing record, provided that they are readily available and are unequivocally linked to the relevant medicinal product. The storage system should ensure that traceability data may be accessed rapidly in case of an adverse reaction from the patient.

By means of a written agreement, the responsibility for the retention of the traceability data may be transferred to the marketing authorisation holder/sponsor.

7. Starting and raw materials

7.1. General principles

The quality of starting and raw materials is a key factor to consider in the production of ATMPs. Particular attention should be paid to avoiding contamination and to minimising as much as possible the variability of the starting and raw materials. Specifications related to the product (such as those in Pharmacopoeia monographs, marketing/clinical trial authorisation), will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked.

The use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells. However, it is stressed that the use of antimicrobials does not replace the requirement for aseptic manufacturing. When antimicrobials are used, they should be removed as soon as possible, unless the presence thereof in the finished product is specifically foreseen in the marketing authorisation/clinical trials authorisation (*e.g.* antibiotics that are part of the matrix of the finished product). Additionally, it is important to ensure that antibiotics or antimicrobials do not interfere with the sterility testing, and that they

are not present in the finished product (unless specifically foreseen in the marketing authorisation/clinical trial authorisation).[12]

7.2. Raw Materials

Raw materials should be of suitable quality having regard to the intended use. In particular, the growth promoting properties of culture media should be demonstrated to be suitable for its intended use.

As far as possible, raw materials used in the manufacturing of ATMPs should take into consideration the *Ph. Eur 5.2.12 general chapter on raw materials of biological origin for the production of cell based and gene therapy medicinal products.* While raw materials should be of pharmaceutical grade, it is acknowledged that, in some cases, only materials of research grade are available. The risks of using research grade materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured). Additionally, the suitability of such raw materials for the intended use should be ensured, including –where appropriate– by means of testing (*e.g.* functional test, safety test).

Specifications for raw materials should be set as explained in Section 6(2). In the case of critical raw materials, the specifications should include quality requirements to ensure suitability for the intended use, as well as the acceptance criteria. These quality requirements should be agreed with the supplier(s) ("agreed specifications"). The assessment whether a specific raw materials is critical should be done by the manufacturer (or, as appropriate, the sponsor or marketing authorisation holder) having regard to the specific risks. The decisions taken should be documented. The agreed 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's materials 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. Reliance on the certificate of analysis of the supplier is acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers). For raw materials that are authorised as medicinal products in the EU (*e.g.* cytokines, human serum albumin, recombinant proteins) the certificate of analysis of the supplier is not required. Where available, the use of authorised medicinal products is encouraged.

The risk of contamination of raw materials of biological origin during their passage along the supply chain must be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform

[12]Ph.Eur. chapter 2.6.1 on sterility testing describes the use of neutralising substances for products containing antibiotics.

Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required.[13] Where there is a potential mycoplasma contamination risk associated with a raw material, the ATMP manufacturer should filter the material prior to use (0.1 μm filter), unless the supplier of the raw material has certified that the raw material has been tested and is mycoplasma free.

The risk of contamination from other materials that come into direct contact with manufacturing equipment or the product (such as media used for process simulation tests and lubricants that may contact the product) should also be taken into account.

Raw materials in the storage area should be appropriately labelled. Labels for critical raw materials 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;
- storage conditions;
- the status of the contents (*e.g.* in quarantine, on test, released, rejected);
- an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label. The use of automated systems (*e.g.* use of barcodes) is permissible.

Only raw materials that have been released by the person responsible for quality control should be used.

The ATMP manufacturer should put in place appropriate measures to ensure that critical raw materials can be traced in order to facilitate recall of products if necessary.

7.3. Starting Materials

The donation, procurement and testing of human tissues and cells used as starting materials should be in accordance with Directive 2004/23/EC. For blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing is likewise acceptable. The accreditation, designation, authorisation or licensing of the supplier of starting materials as provided for under the legislation above-referred should be verified.

When the cells/tissues used are outside the scope of the Directive 2004/23/EC or- as appropriate- Directive 2002/98/EC (e.g. cell-lines/cell banks established outside the EU, or cells procured before the entry into force thereof), the ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder) should take appropriate steps to ensure the quality, safety and traceability thereof, in accordance with the terms of the marketing authorization/clinical trial authorisation.

The ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder) should establish quality requirements for the starting materials (specifications) which should

[13] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf (updated as appropriately).

be agreed with the supplier(s). These agreed specifications should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate. Depending on the product's characteristics, testing in addition to that foreseen in the Directive 2004/23/EC (or- as appropriate- Directive 2002/98/EC) may be required. The agreed specifications should be in compliance with the terms of the marketing authorisation or clinical trial authorisation.

The ATMP manufacturer should verify compliance of the supplier's materials 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 in accordance with Directive 2002/98/EC or Directive 2004/23/EC do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing provided for under the national law of the Member State where the blood/tissue establishment is located. However, if the agreed specifications foresee additional requirements (*e.g.* additional testing), adequate supervision in respect of the additional requirements should be carried out.

In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder) and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting materials, in particular, on tests results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the ATMPs manufactured therefrom.

The risk of contamination of the starting materials during their passage along the supply chain must be assessed, with particular emphasis on viraland microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required.

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

Where the results from the test(s) required to release the starting materials take a long time (*e.g.* sterility test), it may be permissible to process the 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 assessed and understood. In such cases, the finished product should only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are implemented (*see* also Section 11.3.2).

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;
- storage conditions;
- the status of the contents (*e.g.* in quarantine, on test, released, rejected);
- an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label. The use of automated systems (*e.g.* use of barcodes) is permissible.

Processing of starting materials

The quality of ATMPs is largely dependent on the manufacturing process of the starting materials and these activities should take place in a GMP environment.[14]

In the case of cell and tissue-based products, the initial processing steps of the cells/tissues (*e.g.* isolation) are manufacturing activities that should be conducted in accordance with the GMP requirements provided for in these Guidelines, even if it is done by a third party (*e.g.* a tissue establishment or a CMO). The requirements in Section 13 also apply to the outsourcing of the processing activities.

The use of cells that have been separated/isolated and preserved outside a GMP environment for the manufacture of an ATMP should remain exceptional and it is only possible if a risk analysis is performed to identify the testing requirements necessary to ensure the quality of the starting material. The overall responsibility for the quality – as well as the impact thereof on the safety and efficacy profile of the product- lies with the ATMP manufacturer (and/or, as appropriate, the sponsor or marketing authorisation holder), even if the activities have been outsourced. The release of such cells/tissues for use in the manufacturing process should be done by the person responsible for quality control after verifying the quality and safety thereof. Additionally, the competent authorities should agree to the control strategy in the context of the assessment of the marketing authorisation application/clinical trial authorisation application.

In the case of vectors and naked plasmids used as starting materials for the manufacturing of gene therapy medicinal products, the principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.

Additional considerations for xenogeneic cells and tissues:

The use of xenogeneic cells/tissues in the manufacture of ATMPs poses additional risks of transmitting known and unknown pathogens to humans, including the potential risk of introducing new infectious diseases. The selection of donor animals must therefore be strictly controlled. Source/donor animals should be healthy and should be specific pathogen free (SPF) and be raised in SPF conditions, including health monitoring. The donor/source animal

[14]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.

should have been bred in captivity (barrier facility) specifically designed for this purpose. In the manufacture of ATMPs, it is not acceptable to use xenogeneic cells and tissues from wild animals or from abattoirs. Cells and tissues of founder animals similarly should not be used.

Appropriate measures should be implemented to identify and prevent incidents that negatively affect the health of the source/donor animals or that could negatively impact on the barrier facility or the SPF status of the source/donor animals. In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored and recorded. Specialist advice should be obtained in establishing the monitoring program.

Instances of ill-health occurring in the herd should be investigated with respect to the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing). The decisions taken must be documented. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced cells/tissues have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation.

The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

8. Seed lot and cell bank system

It is recommended that the system of master and working seed lots/cell banks is used for allogeneic products which do not require a match between the donor and the patient. However, the establishment of seed lots/cell banks is not mandatory.

When seed lots and cell banks, including master and working generations are used, they should be established under appropriate conditions, including compliance with GMP as provided for in these Guidelines. This should include an appropriately controlled environment to protect the seed lot and the cell 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.

The number of generations (doublings, passages) 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.

However, it is acknowledged that comprehensive information may not be available for seed lots and cell banks established in the past (*i.e.* prior to the entry into force of Regulation

1394/2007). The use of starting materials coming from such seed lots/cell banks can only be accepted in exceptional cases and provided that there is extensive characterisation to compensate for the missing information. Additionally, the competent authorities should agree to the strategy in the context of the assessment of the marketing authorisation application/clinical trial authorisation application.

Cell bank safety testing and characterisation are important for batch-to-batch consistency and to prevent contamination with adventitious agents. 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/cells in the same area or equipment should prevent mix-up and take account the infectious nature of the materials to prevent cross-contamination.

Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be continuously monitored and records retained. Depending on criticality, alarm systems should be considered. Where used, the liquid nitrogen level should also be monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

Following the establishment of cell banks and master and viral seed lots, quarantine and release procedures should be followed. Evidence of the stability and recovery of seeds and banks should be documented and records should be kept in a manner permitting trend evaluation. In the case of investigational ATMPs, a gradual approach is acceptable. Thus, preliminary stability data (*e.g.* from earlier phases of development or from suitable cell models) should be available before the product is used in a clinical trial, and the stability data should be built-up with real-life data as the clinical trial progresses.

Containers removed from the cryostorage unit, can only be returned to storage if it can be documented that adequate conditions have been maintained.

Access to cell banks should be limited to authorised personnel.

Cell Stock

Cell-based products are often generated from a cell stock obtained from a 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 (including introduction of cells from new donors) should be addressed in the marketing authorisation/clinical trial authorisation and the conditions therein should be complied with.

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.

When cell stocks are used, the handling, storage and release of cells should be done in accordance with the principles outlined above for cell banks.

Cell stocks/banks and viral seed stocks established in the past outside of GMP conditions

The establishment of new cell stocks/banks and viral seed stocks should be done in accordance with GMP. 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 in the past without full GMP compliance. In these cases, a risk analysis should be conducted to identify the testing requirements necessary to ensure the quality of the starting material. In all cases, the overall responsibility for the quality – as well as the impact thereof on the safety and efficacy profile of the product- lies with the ATMP manufacturer and/or -as appropriate- the sponsor or marketing authorisation holder.

The use of starting materials from cell stocks/cell banks and viral seed stocks generated in the past (*i.e.* prior to the entry into force of Regulation 1394/2007) outside of GMP conditions should be approved by the competent authorities in the context of the assessment of the marketing authorisation application/clinical trial authorisation application.

9. Production

9.1. General principles

Production operations, including filling, packaging and -as applicable- cryopreservation 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 authorization.

In case of investigational ATMPs, the knowledge and understanding of the product may be limited, particularly for early phases of clinical trials (phase I and I/II). It is therefore acknowledged that the manufacturing process (including quality controls) may need to be adapted as the knowledge of the process increases. In the early phases of development, it is critical to carefully control and document the manufacturing process. It is expected that the manufacturing process and quality controls become more refined as development progresses.

Manufacturing processes and their control strategies should be reviewed regularly, and they should be improved as appropriate. While this is especially relevant during the early phases of clinical trials, it is also 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 process is adopted, steps should be taken to demonstrate its suitability. 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. Any change to the manufacturing formula or manufacturing method should be managed in accordance with the principles set out in Section 6(2).

Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a responsible person (after having assessed the impact thereof on quality, safety and efficacy), with the involvement of the QP as

appropriate. Deviations should be investigated with a view to identify the root cause and to implement corrective and preventive measures as appropriate.

9.2. Handling of incoming materials and products

All handling of materials and products (such as receipt and quarantine, sampling, storage, labelling and packaging) should be done in accordance with written procedures or instructions and recorded as appropriate. The control strategy should be adequate having regard to the risks.

All incoming materials should be checked to ensure that the consignment corresponds to the order. The specific requirements for raw and starting materials are described in Section 7. For other materials, reliance on the documentation provided by third parties (*e.g.* supplier) is acceptable provided that all risks are duly understood and that appropriate measures are put in place to eliminate the risks or mitigate them to an acceptable level (*e.g.* qualification of suppliers). Where necessary, identity verification and/or testing should be considered.

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 purchased as such should be released by the person responsible for quality control before they can be used in production, after verification of compliance with the relevant specifications.

All materials and products should be stored under appropriate conditions to ensure the quality and in an orderly fashion to permit batch segregation and stock rotation. Particular attention should be paid to implementing appropriate measures to prevent mix-ups of autologous products and other dedicated products (*i.e.* products intended for specific patients).

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. 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 storage or processing conditions (*e.g.* ultra-low storage temperatures, waterbath) should be verified.

Containers should be cleaned where necessary. 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 responsible for quality control.

9.3. Utilities

9.3.1. Water

Water used in the manufacturing of ATMPs should be of appropriate quality and regular checks should be carried out to verify the absence of contamination (chemical and biological and, as appropriate, from endotoxins).

Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. In the case of water for injections generated at the site, special attention should be paid to prevention of microbial growth, for example by constant circulation at a temperature above 70˚C.

Water for injections pipes, purified water piping 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. After any chemical sanitisation of a water system, a validated rinsing procedure should be followed to ensure that the sanitising agent has been effectively removed.

The use of pre-packaged water for injections compliant with the European Pharmacopeia[15] removes the need for demonstrating the appropriateness of the quality of the water for injections as provided for in the previous paragraphs.

9.3.2. Medical gases

Gasses used in the production of ATMPs should be of suitable quality.

Where possible, gasses that come into direct contact with the product during processing should be compliant with the European Pharmacopoeia. The use of gasses of technical grades (*i.e.* non-EP compliant) should be supported by a risk-analysis and it should be demonstrated that they are of appropriate quality.

Gasses taken into the aseptic work place or that come into contact with the product should be passed through sterilising filters. The integrity of critical gas filters should be confirmed at appropriate intervals that should be scientifically justified. For batches destined to more than one patient, it is generally expected that the critical gas filter filters will be tested prior to batch release. Liquid nitrogen used for storage of cells in closed containers need not be filtered.

9.3.3. Clean steam

Water used in the manufacture of clean steam should be of appropriate quality. Steam used for sterilisation should be of suitable quality and free from additives at a level that could cause contamination of the product or equipment.

[15] Monograph 0169.

9.4. Prevention of cross-contamination in production

Before any manufacturing operation starts, 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. Mix-ups of materials should be prevented; special precautions should be taken to avoid the mixing of autologous materials or other dedicated materials.

At every stage of production, products and materials should be protected from microbial and other contamination (*e.g.* pyrogens/endotoxins as well as particulate matter (glass and other visible and sub-visible particles)). Appropriate measures should also be put in place to protect 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).

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) and manufacturing process (*e.g.* the use of processes that provide extraneous microbial contaminants the opportunity to grow). If sterilisation of the finished product is not possible, particular attention should be paid to the manufacturing steps where there is exposure to the environment (*e.g.* filling).

In all manufacturing steps that may lead to unwanted formation of aerosols (*e.g.* centrifugation, working under vacuum, homogenisation, sonication) appropriate mitigation measures should be implemented to avoid cross-contamination. Special precautions should be taken when working with infectious materials.

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) Segregated premises.

(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 air-locks and pressure cascade to confine potential airborne contaminant within a specified area.

(v) Utilisation of single use disposable technologies.

(vi) Adequate cleaning procedures. The cleaning procedure (technique, number of sanitation steps, *etc.*) should be adapted to the specific characteristics of the product and of the manufacturing process. A risk-assessment should be used to determine the

cleaning/decontamination procedures that are necessary, including the frequency thereof. As a minimum, there should be appropriate cleaning/decontamination between each batch. The cleaning/decontamination procedures should be validated as explained in Section 10.2.

(vii) Other suitable technical measures, such as the dedication of certain parts of equipment (*e.g.* filters) to a given type of product with a specific risk profile.

(viii) Other suitable organizational measures, such as keeping specific protective clothing inside areas where products with high-risk of contamination are processed, implementing adequate measures to handling waste, contaminated rinsing water and soiled gowning, or imposing restrictions on the movement of personnel.

The control strategy is multifaceted and should address all the potential risks, including therefore measures at the level of the facilities, equipment and personnel, controls on starting and raw materials, implementation of effective sterilisation and sanitisations procedures, and adequate monitoring systems. The totality of the measures applied should assure the absence of contamination of the products manufactured within the manufacturing site. Sole reliance should not be placed on any terminal process or finished product test.

The effectiveness of the measures implemented should be reviewed periodically according to set procedures. This assessment should lead to corrective and preventive actions being taken as 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, as well as the risks attached to the relevant biological materials.

9.5. Aseptic manufacturing

9.5.1. General principles

The majority of ATMPs cannot be terminally sterilised. In such cases, the manufacturing process should be conducted aseptically (*i.e.* under conditions which prevent microbial contamination). In particular, this requires that, for any manufacturing activity that may expose the product to a risk of contamination, the following measures should be implemented:

(i) Manufacturing should take place in clean areas of appropriate environmental cleanliness level. Specifically:

- Production in a closed system, in a closed isolator, or (open) positive pressure isolators: a background clean area of grade D is acceptable.

  Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, disinfection regime of the isolator, the transfer process, and the isolator's integrity.

Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system. The transfer of materials into and out of the isolator is one of the greatest potential sources of contamination and appropriate control measures should be put in place.

When materials are added/withdrawn from the closed system without aseptic connectors (*e.g.* use of filters), the system can no longer be considered closed.

In exceptional circumstances and provided that it is duly justified (*e.g.* manufacturing takes place in the operating theatre and it is not possible to move the production to an outside clean room because the time between the donation and administration of the product is very short and the patient is also in the operating theatre waiting for administration of the ATMP) closed systems may be placed in a controlled but non-classified environment. The conditions of the operating theatre where the manufacturing activity takes place should be adequate and sufficient to ensure the quality and safety of the product. It is stressed that this is only acceptable in exceptional cases and that the product should not be exposed at any moment to the environment (*e.g.* supporting data from leak testing and pressure check of the equipment). Additionally, it should be demonstrated that the expected clinical benefit for the patient outweighs the risks linked to the absence of a classified background.

- Production in an open system: In general, when the product is exposed to the environment (*e.g.* working under laminar air flow), a critical clean area of grade A with a background clean area of grade B is required for manufacturing steps and filling.

  However, a background clean area of grade C could be justified if there are further microbial contamination controls downstream, *e.g.*:
  - Preparation of solutions which are to be sterile filtered during the process can be done in a clean area of grade C.
  - For the manufacturing process of viral vectors, the following considerations apply:
    - The expansion phase before the sterilising filtration can be performed in a critical clean area of grade A with a background clean area of grade C.
    - The sterilising filtration and filling needs to be performed in a critical clean area of grade A with a background clean area of grade B, unless a closed system with aseptic connectors is used.

  In the case of investigational ATMPs used in first-in-man clinical trials, alternative approaches may be possible under the conditions explained in Section 2.3.4.

- Use of semi-closed technologies (*e.g.* processing inside sterile disposable kits, incubation in closed flasks, bags or fermenters[16]): a background C may be acceptable if adequate control measures are implemented to avoid the risk of cross-contamination (*e.g.* appropriate control of materials, personnel flows and cleanness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher grade.

- Terminally sterilised ATMPs: For ATMPs that can be terminally sterilised, the preparation of solutions and components for subsequent filling should be done in at least a grade D environment in order to reduce the risk of microbial and particulate contamination. However, a grade C environment should be used where the product is at a high risk of microbial contamination (*e.g.* the product actively supports microbial growth or must be held for a long period before sterilisation).

  Filling operations should take place in a C environment, unless the product is at a high risk of contamination from the environment (*e.g.* the filling operation is slow, the container is wide-necked, the production is held for a long time prior to terminal sterilisation, or the product is exposed for more than a few seconds to the environment). In such cases, the filling should be done in a critical clean area of grade A with a background clean area of (at least) grade C.

(ii) Materials, equipment and other articles that are introduced in a clean area should not introduce contamination. To this end, the use of double-ended sterilisers sealed into a wall or other effective procedures (*e.g.* H2O2 locks) should be used.

Sterilisation of articles and materials elsewhere is acceptable provided that the sterilisation process is validated and there are multiple wrappings (if possible, in numbers equal -or above- the number of stages of entry to the clean area), and enter through an airlock with the appropriate surface sanitization precautions. Unless culture media is delivered ready-to-use (*i.e.* already sterilised by the supplier), it is recommended that media is sterilised *in situ*.

When sterilisation of articles, materials or equipment is not possible, a strictly controlled process should be implemented to minimise the risks (*e.g.* treatment of biopsy with antibiotics, sterile filtration of raw materials, appropriate disinfection of materials). The effectiveness of the process should be checked at appropriate intervals.

(iii) 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. In-line sterilising filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, *etc.* to bioreactors should be used where possible.

[16] If the closed flasks, bags, fermenters allow for a full isolation of the product from the environment, these would be considered as closed systems and the relevant principles of closed systems would apply.

The conditions for sample collection, additions and transfers involving replication competent vectors or materials from infected donors should prevent the release of viral/infected material.

9.5.2. Aseptic processing validation

The validation of aseptic processing should include a process simulation test. The aseptic process simulation test is the performance of the manufacturing process using a sterile microbiological growth medium and/or placebo (*e.g.* culture media of cells which is demonstrated to support the growth of bacteria) to test whether the manufacturing procedures are adequate to prevent contamination during production. Results and conclusions should be recorded. The process simulation test should follow as closely as possible the routine manufacturing process and it should be conducted in the same locations where the production occurs. The process simulation should focus on all operations carried out by operators involving open process steps. All potential interventions and challenges to the process (*e.g.* work overnight) should be considered.

An appropriate simulated model (*e.g.* use of alternative tools to the manufacturing kit ("mock materials") may be acceptable provided that this is duly justified.

Alternative approaches may also be developed for steps that take a long time. The simulation of reduced times for certain activities (*e.g.* centrifugation, incubation) should be justified having regard to the risks. In some cases, it may also be acceptable to split the process into key stages which are simulated separately provided that the transitions between each stage are also evaluated. When a closed system is used for the manufacturing of an ATMP, the process simulation should focus on the steps related to the connections to the closed system.

In case of manufacturing of various types of ATMPs, consideration can be given to the matrix and/or bracketing approach. Under a bracketing approach, only samples on the extremes of certain design factors would undergo a full process simulation. This approach can be accepted if the handling of different products is similar (same equipment and processing steps). Under a matrix approach, it may be possible to combine media fills for different ATMPs sharing similar processing steps, provided that the worst case is covered by the matrix approach. The use of bracketing and matrixing together should be duly justified.

Filled containers should be inverted to ensure the media/placebo touches all parts of the container/closure and should be incubated. The selection of the incubation duration and temperature should be justified and appropriate for the process being simulated and the selected media/placebo.

All contaminants from the filled containers should be identified. The results should be assessed, in particular in relation to the overall quality of the product and the suitability of the production process. The target should be zero growth. Any growth detected should be investigated. If the growth detected is indicative of potential systemic failure, the potential impact on batches manufactured since the last successful media fill simulation test should be assessed and adequate corrective and preventive actions should be taken.

Process simulation test to support initial validation should be performed with three consecutive satisfactory simulation tests per production process.

Process simulation (one run) should be repeated periodically to provide ongoing assurance of the ability of the process and the staff to ensuring aseptic manufacturing. The frequency should be determined based on a risk assessment but should generally not be lower than once every six months (for each production process). However, lower frequency may be acceptable in the following cases:

(i) Infrequent production (i.e. if the interval between the production of two batches is more than six months): the process simulation test can be done just before the manufacturing of the next batch, provided that the results of the process simulation test are available prior to the starting of production. However, in cases of long periods of inactivity (i.e. over one year), the validation prior to restart of production should be done with three runs.

(ii) Production of autologous products (or allogeneic product in a matched scenario) where every unit is tested for sterility as part of the batch release controls: the process simulation test can be done annually, provided that the results of the sterility test are available prior to the administration of the product to the patient.

When considering the frequency of the simulation test, the manufacturer is required to consider also the relevance of the media fill test for the training of operators and their ability to operate in an aseptic environment (*see* Section 3.2).

A process simulation should also be conducted in cases when there is any significant change to the process *(e.g.* modification of HVAC system, equipment, *etc*). In this case, three runs are required.

9.5.3. Sterilisation

The sterilisation processes applied should be suitable having regard to the specific characteristics of the product. In particular, where the sterilisation of the starting materials (*e.g.* chemical matrixes) and raw materials and excipients is required, it should be ensured that the sterilisation process applied *(e.g.* heat, irradiation, filtration, or chemical inactivation) is effective in terms of removing the contaminants while preserving the activity of starting/raw materials and excipients

The sterilisation process(es) applied should be validated. Particular attention should be paid when the adopted sterilisation method is not in accordance with the European Pharmacopoeia. Additional guidance on sterilisation methods can be found in Annex 1 of the Part I of the Good Manufacturing Practice Guidelines published in Volume 4 of Eudralex.

Solutions or liquids that cannot be sterilised in the final container should be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container.

The filter should not have a negative impact on the product (*e.g.* by removing components or by releasing substances into it). The integrity of the sterilising filter should be verified before use, in case it is suspected that the filter may have been damaged by processing, and should also be confirmed by on-line testing immediately after use by an appropriate method (*e.g.* bubble point, diffusive flow, water intrusion or pressure hold test). If filter integrity cannot be tested (*e.g.* small size batches), an alternative approach may be applied, which should be based on a risk-assessment. The same filter should not be used for different batches. Additionally, the same filter should not be used for more than one working day, unless such use has been validated.

9.6. Other operating principles

Critical quality parameters (as identified in the marketing authorisation/clinical trial authorisation) should be monitored at appropriate intervals. When technically possible, continuous monitoring of key process parameters is expected (*e.g.* in bioreactors). Any deviations should be recorded and investigated, and the measures taken should also be documented.

Any necessary environmental controls (*see* Section 4.3.3) should be carried out and recorded.

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. Any such re-usage should be supported by appropriate validation data. Acceptance criteria, operating conditions, regeneration methods, life span, and sanitization or sterilization methods of chromatography columns should be defined.

Where ionizing radiation is used in the manufacturing of ATMPs, Annex 12 of the Part I of the Good Manufacturing Practice Guidelines published in Volume 4 of Eudralex should be consulted for further guidance.

9.7. Packaging

The suitability of primary packaging materials should be ensured having regard to the characteristics of the product and the storage conditions (*e.g.* products that should be stored at ultra-low temperature). The specifications provided for in the marketing authorisation or the clinical trial authorisation should be complied with.

The level of documentation regarding the demonstration of suitability of the primary packaging material should be adapted to the phase of development. For production of authorised ATMPs, selection, qualification, approval and maintenance of suppliers of primary packaging materials should be documented.

ATMPs should be suitably packaged to maintain the quality of the product during storage, handling, and shipping. Particular attention should be paid to the closure of containers so as to ensure the integrity and quality of the product. For authorised ATMPs, the closure

procedures should be validated and the effectiveness should be verified at appropriate intervals. Validation with surrogate materials is acceptable when materials are scarce.

Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly. Labels should be compatible with transport and storage conditions (*e.g.* ultra-low temperatures).

Prior to product labelling operations, the work area and any equipment used should be clean and free from any product, material or document that is not required for the current operation. Precautions should be taken to avoid mix-ups of products and to protect the product from the risk of contamination.

9.8. Finished products

As a general principle, finished products should be held in quarantine until their release under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation. It is acknowledged, however, that due to the short shelf-life, physical or administrative quarantine of ATMPs may not always be possible. The release of products before completion of all quality control tests is addressed under Section 11.3.2.

Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When the inspection is done visually, it should be done under suitable conditions of illumination and background.

Any defect detected should be recorded and investigated. The requirements laid down in Section 14.1 are also applicable in case of defects detected at this stage.

Finished products should be stored under adequate conditions to preserve the quality of the product and to prevent mix-ups. Particular attention should be paid to implementing appropriate measures to prevent mix-ups of autologous products and other dedicated products (*i.e.* products intended for specific patients).

9.9. Rejected, recovered and returned materials

Rejected materials should be clearly marked as such and stored separately in restricted areas *(e.g.* locked). Starting and raw materials should either be returned to the suppliers or, removed from the production environment. Whatever action is taken, it should be approved and recorded by authorized personnel.

The reprocessing of rejected products should be exceptional. For authorised ATMPs, reprocessing is only permissible if this possibility is contemplated in the marketing authorisation. In the case of investigational ATMPs, the competent authorities should be informed when, exceptionally, there is reprocessing.

Additionally, the use of reprocessed materials is only possible if the quality of the final product is not affected and the specifications are met. The need for additional testing of any finished product which has been reprocessed, or into which a reprocessed product has been

incorporated, should be evaluated by the person responsible for quality control. Records should be kept of the reprocessing. Certification by the QP is required before the product is released.

Returned products, which have left the control of the manufacturer, should be marked as such and be segregated so that they are not available for further clinical use, unless without doubt their quality is satisfactory after they have been critically assessed by the person responsible for quality control.

10. Qualification and validation

10.1. Qualification of premises and equipment

10.1.1 General principles

Premises and equipment used in the manufacture of ATMPs should be qualified. Through the qualification of premises and equipment, it is established that the premises and equipment are adequate for the intended operations.

Decisions on the scope and extent of the qualification should be based on a risk-assessment, which should be documented. The following should be considered when defining the strategy to the qualification of premises and equipment:

- Clean areas should be qualified in accordance with ISO 14644-1 and re-qualified at appropriate intervals in accordance with ISO 14644-2. In particular, periodic classification testing (in accordance with ISO 14664-1) is expected annually but the frequency can be extended based on risk assessment, the extent of the monitoring system and data that are consistently in compliance with acceptance limits or levels defined in the monitoring plan.

- If computerized systems are used, their validation should be proportionate to the impact thereof on the quality of the product.[17] For computerised systems supporting critical processes, provisions should be made to ensure continuity in the event of a system breakdown (*e.g.* a manual or alternative system).

- For investigational ATMPs, it is expected that at least the suitability of the air quality system (in accordance with ISO 14644-1 and ISO 14664-2) and the suitability of the premises to adequately control the risk of microbial and non-viable particle contamination is verified. Any other aspect of the premises that is critical having regard to the specific risks of the intended manufacturing process should be qualified (*e.g.* containment measures when viral replicating vectors are used). Critical equipment should be qualified also.

Before starting the manufacturing of a new type of ATMP in premises that have already been qualified, the manufacturer should assess if there is a need for re-qualification having regard

[17] Principles relevant to the validation of computer equipment are laid down in Annex 11 of the Part I of the Good Manufacturing Practice Guidelines published in Volume 4 of Eudralex. The elements described therein are guiding principles that may be adapted as necessary.

to the specific risks and characteristics of the new manufacturing process/new product. For example, if the premises have been qualified for open processing and a closed system is introduced, it can be assumed that the (existing) qualification of the premises covers a worst case scenario and therefore no re-qualification is needed. In contrast, when the premises have been qualified for a simple manufacturing process and a more complex process is introduced that *e.g.* may require an additional level of containment, requalification is required. Likewise, if there is a significant change in the lay out of the premises, there should be an assessment whether requalification is required

Facilities and equipment should be re-evaluated at appropriate intervals to confirm that they remain suitable for the intended operations.

10.1.2. Steps of the qualification process

The qualification strategy should follow the following steps:

(a) Setting the user requirement specifications: The manufacturer, or- as appropriate- the sponsor or marketing authorisation holder should define the specifications for the premises and equipment. The user requirement specifications should ensure that the critical quality attributes of the product and the identified risks linked to the manufacturing processes are adequately addressed *(e.g.* measures to avoid cross-contamination in a multi-product facility). The suitability of the materials of the parts of the equipment that come into contact with the product should be also addressed as part of the user requirement specifications.

(b) Verifying compliance with the user requirement specifications: The manufacturer or- as appropriate- the sponsor or marketing authorisation holder should verify that the premises/equipment comply with the user specifications and are in line with GMP requirements. Typically, this involves the following steps:

(i) *Installation Qualification (IQ):* As a minimum, it should be verified that:

- components, equipment, pipe work and other installations have been installed in conformity with the user specifications,
- operating and maintenance instructions are provided (as appropriate),
- instruments are appropriately calibrated and –where applicable- associated alarms are functional.

(ii) *Operational Qualification (OQ*): The suitability of the premises and equipment to operate as designed (including under "worst case" conditions) should be tested.

(iii) *Performance Qualification (PQ):* The suitability of the premises and equipment to operate consistently in accordance with the requirements of the intended manufacturing process (assuming worst case conditions) should be tested. A test with surrogate materials or simulated product is acceptable.

Any deviations identified should be addressed before moving to the next qualification step. However, it is acknowledged that, in some cases, it may be appropriate to concurrently perform IQ, OQ and PQ. It may also be acceptable to perform the process validation concurrently with the PQ.

Where functionality of the equipment is not affected by transport and installation, the documentation review and some tests could be performed at the vendor's site (*e.g.* through factory acceptance testing), without the need to repeat the relevant elements of IQ/OQ at the manufacturer's site.

Likewise, when validating several identical pieces of equipment, it is acceptable for the manufacturer to establish a suitable testing strategy based on an evaluation of the risks.

(c) Documentation: A report should be written summarizing the results and conclusions reached. When qualification documentation is supplied by a third party (*e.g.* vendor, installers), the ATMP manufacturer or -as appropriate- the sponsor or marketing authorisation holder should assess whether the documentation provided is sufficient, or if additional tests should be performed at the site to confirm suitability of the equipment (*e.g.* when information gaps exist having regard to the intended manufacturing process, if the equipment is to be used differently than as intended by the manufacturer of the equipment, *etc*.)

Where the qualification of the premises/equipment is outsourced to a third party, the principles laid down in Section 13 also apply.

10.2. Cleaning validation

The cleaning procedures applied to re-usable tools and parts of equipment that enter into contact with the product should be validated.

Cleaning validation is the documented evidence that a given cleaning procedure effectively and reproducibly removes contaminants, residues from previous product, and cleaning agents below a pre-defined threshold. There may be more than one way to perform cleaning validation. The objective is to demonstrate that the cleaning process consistently meets the predefined acceptance criteria. The risk of microbial and endotoxin contamination should be duly assessed.

The following considerations apply when designing the cleaning validation strategy:

- Factors that influence the effectiveness of the cleaning process (*e.g.* operators, rinsing times, cleaning equipment and amounts of cleaning agents used) should be identified. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

- The influence of the time between manufacture and cleaning, and between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process..

- When justified due to the scarcity of the starting materials, simulating agents may be used.

Cleaning procedures for closely related ATMPs do not need to be individually validated. A single validation study which considers the worst case scenario is acceptable.

Cleaning validation should be described in a document, which should cover:

(i) *Detailed cleaning procedure for each piece of equipment:* Grouping approaches[18] are acceptable if appropriately justified (*e.g.* cleaning of processing vessels of the same design but with different capacity). Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected. The selection of the equipment should be representative of the worst case scenario (for example, the higher capacity vessel).

(ii) *Sampling procedures*: Sampling may be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. For swabs, sampling should be from locations identified as "worst case". Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

(iii) *Validated analytical methods to be used*.

(iv) *Acceptance criteria*, including the scientific rationale for setting the specific limits.

The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated (usually three consecutive batches as a minimum). Cleaning validation may be reduced or not required if only disposables are used in the manufacturing process.

A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. However, it is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach either.

<u>Approach for investigational ATMPs</u>

For investigational ATMPs, cleaning verification is acceptable. In such cases, there should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

[18] The design assumes that validation of any intermediate levels is represented by validation of the extremes.

10.3. Process validation

Process validation is the documented evidence that the manufacturing process can consistently produce a result within specific parameters. While it is acknowledged that some degree of variability of the finished product due to the characteristics of the starting materials is intrinsic to ATMPs, the aim of the process validation for ATMPs is to demonstrate that the finished product characteristics are within a given range (in compliance with the terms of the marketing authorisation).

The strategy to process validation should be laid down in a document ("validation protocol"). The protocol should define (and justify as appropriate) the critical process parameters, critical quality attributes and the associated acceptance criteria based on development data or documented process knowledge. The approach retained should be justified. As appropriate, the protocol should identify other (non-critical) attributes and parameters which should be investigated or monitored during the validation activity, and the reasons for their inclusion.

The following should also be specified in the protocol:

- List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status.
- List of analytical methods and how they are to be validated, as appropriate.
- Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected.
- Where required, additional testing to be carried out with acceptance criteria.
- Sampling plan and the rationale behind it.
- Methods for recording and evaluating results.
- Process for release and certification of batches (if applicable).
- Specifications for the finished product (as provided for in the marketing authorisation).

It is generally accepted that, as a minimum, three consecutive batches manufactured under routine conditions constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used, whether similar products or processes are already used at the site, the variability of starting material (autologous v. allogenic), clinical indication (rare disease: only few batches will be produced).

The limited availability of the cells/tissues which is typical for most ATMPs requires the development of pragmatic approaches. The approach to process validation should take into account the quantities of tissue/cells available and should focus on gaining maximum experience of the process from each batch processed. Reduced process validation should, where possible, be offset by additional in-process testing to demonstrate consistency of production.

- Validation with surrogate materials: The use of surrogate material may be acceptable when there is shortage of the starting materials (*e.g*. autologous ATMPs, allogeneic in a matched-donor scenario, allogeneic where there is no expansion of cells to MCB). The representativeness of surrogate starting material should be evaluated, including - for example- donor age, use of materials from healthy donors, anatomical source (*e.g.* femur *vs.* iliac crest) or other different characteristics (*e.g.* use of representative cell-types or use of cells at a higher passage number than that foreseen in the product specifications).

  Where possible, consideration should be given to complementing the use of surrogate materials with samples from the actual starting materials for key aspects of the manufacturing process. For instance, in the case of an ATMP based on modification of autologous cells to treat a genetic disorder, process validation using the autologous cells (affected by the condition) may be limited to those parts of the process that focus on the genetic modification itself. Other aspects could be validated using a representative surrogate cell type.

- Concurrent validation approaches: Due to the limited availability of the starting materials and/or where there is a strong benefit-risk ratio for the patient, a concurrent validation may be acceptable. The decision to carry out concurrent validation should be justified. Regular reviews of data from the manufacture of batches should be subsequently used to confirm that the manufacturing process is able to ensure that the specifications in the clinical trial/marketing authorization are complied with.

  Where a concurrent validation approach has been adopted, there should be sufficient data to support the conclusion that the batch meets the defined criteria. The results and conclusion should be formally documented and available to the QP prior to the certification of the batch.

- Process validation for closely related products where the same manufacturing process is used (*e.g.* autologous T-cell based ATMPs, viral vectors manufactured according to the same manufacturing process): the validation of the process does not need to be repeated for each of the products, in so far as the manufacturing process remains the same.

Investigational ATMPs

The manufacturing process for investigational ATMPs is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation. Additionally, it is expected that the aseptic processes (and, where applicable, sterilising processes) have been validated.

Process validation/evaluation data should be collected throughout the development. It is noted that for the clinical trial to be used in support of a marketing authorisation application it is important to demonstrate that the manufacturing process of the investigational ATMP ensures consistent production.

10.4. Validation of test methods.

The validation of analytical methods is intended to ensure the suitability of the analytical methods for the intended purpose. Analytical procedures, which are either described in the European Pharmacopoeia, the pharmacopoeia of a Member State, or are linked to a product specific monograph, and are performed according to the monograph, are normally considered as validated. In such cases, the suitability of the validated test for the intended purpose should be verified.

All analytical methods should be validated at the stage of marketing authorisation application.

Investigational ATMPs

During clinical development a gradual approach can be applied:

- First-in-man and exploratory clinical trials: Sterility and microbial assay should be validated. In addition, other assays that are intended to ensure patient's safety should also be validated (*e.g.* when retroviral vectors are used, the analytical methods for testing for replication competent retrovirus should be validated).

- Throughout the clinical development, the suitability of analytical methods used to measure critical quality attributes (*e.g.* inactivation/removal of virus and/or other impurities of biological origin) should be established but full validation is not required. Potency assays are expected to be validated prior to pivotal clinical trials.

- Pivotal clinical trials: Validation of analytical methods for batch release and stability testing is expected.

10.5 Validation of transport conditions

Transport conditions may have a crucial impact on the quality of ATMPs. The transport conditions should be defined in writing.

The adequacy of the defined transport conditions (*e.g.* temperature, type of container, *etc.*) should be demonstrated.

Compliance with the defined transport conditions falls outside the responsibility of the manufacturer (unless such responsibility is assumed by means of contract). Such compliance is outside the scope of GMP.

11. Qualified person and batch release

11.1. General principles

Each manufacturing site in the EEA must have at least one Qualified Person ("QP").[19] It is not excluded that two or more sites may have the same QP, provided that this does not impair the ability of the QP to provide his services to each of the sites in a continuous fashion.

Without prejudice to Section 11.5, batches of medicinal products should only be released for sale, 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 computerized systems). When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.

11.2. Qualified person

In addition to having the qualification requirements provided for under Article 49 of Directive 2001/83, QPs responsible for ATMPs should have training and experience relevant to the specific characteristics of these products, including cell and tissue biology, biotechnological techniques, cell processing, characterization and potency testing. QPs should have detailed knowledge of the product type and manufacturing steps for which they are taking responsibility.

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

QPs should have access to:

- the necessary details of the marketing authorisation/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.

<u>Imported ATMPs</u>

[19] 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), as amended. *See* also Article 61(2)(b) of Regulation (EU) No 536/2014.

In case of imports of investigational ATMPs from third countries, the QP should ensure that the quality of the batch is in accordance with the terms of the clinical trial authorisation (including compliance with the terms of the Product Specification File) and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EU.[20]

In case of imports of authorised ATMPs from third countries, the QP should 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 substance(s) as well as any other necessary checks.[21] However, it is acknowledged that for ATMPs it is not always possible to separate the active substance from the finished product. The re-testing strategy should be in accordance with the terms of the marketing authorisation.

Additionally, it may be justified to rely on testing performed in the third country in cases where the limited amount of material available (*e.g.* autologous products) or the short shelf-life impedes double release testing. In such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs) or under GMP conditions equivalent to those applicable in the EU (in the case of investigational ATMPs).

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.

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 in 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 also apply.

The QP should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.

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

[20] Article 62 and 63(3) of Regulation (EU) No 536/2014.
[21] Article 51(1)(b) of Directive 2001/83/EC.

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 in 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.

The QP should have access to any documentation relevant to the task for which they are talking responsibility.

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/clinical trial authorisation,
- the specifications for the raw materials, starting materials (including matrixes or devices that are a component of the ATMP) and packaging materials comply with the terms of the marketing authorisation/clinical trial authorisation,
- in case of autologous products (or donor-matched scenario), the match between the origin of the starting material and the recipient has been verified (information on the origin of the cells/tissues should be checked),
- the excipients used in the manufacturing of the finished product are of suitable quality and that they have been manufactured under adequate conditions,
- for combined ATMPs, the medical device(s) used comply with the relevant general safety and performance requirements provided for under the EU legislation on medical devices, and are adequate for the use in the combined ATMP,
- where relevant, the viral and microbial safety and TSE status of all materials used in batch manufacture is compliant with the terms of the marketing authorisation/clinical trial authorisation,
- all required in-process controls and checks (including environmental monitoring) have been made and appropriate records exists,
- finished product quality control test data complies with the relevant specifications,
- on-going stability data continues to support certification,

- the impact of any deviation 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 applicable.[22]

While the QP has responsibility for ensuring that the above verifications are done, these tasks may be delegated to appropriately trained personnel or third parties.

In the case of investigational ATMPs, the amount of relevant information available will depend on the stage of development (*e.g.* medical devices used in an investigational combined ATMP may be in an investigational phase as well and, in such cases, the role of the QP is to ensure that the quality specifications set by the manufacturer are respected). 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/clinical trial authorisation, and all other relevant regulatory requirements, including GMP.

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, 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.

(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.

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

[22] ATMPs that contain or consist of tissues or cells are exempted from the safety feature in accordance with Commission delegated Regulation (EU) 2016/161 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use, (OJ L32, 9.2.2016, p. 1).

Additional considerations for investigational ATMPs

Investigational ATMPs should remain under the control of the sponsor until after completion of a two-step procedure: certification by the QP and release by the sponsor for use in a clinical trial. The process of release of the product for use in the clinical site should be agreed between the sponsor and the manufacturer taking into account the shelf-life of the product. Both steps should be documented as appropriate.

Transfers of the investigational ATMPs from one trial site to another should remain the exception. When they occur, the QP –in agreement with the sponsor– should establish the specific conditions under which the transfers should take place.

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

- Assessment by a designated person(s) of the batch processing records, results from environmental monitoring (where available) and the available analytical results for review in preparation for the initial certification by the QP, which allows release for administration.

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

The delegation of tasks to the designated person(s) and the description of the batch certification and release procedure should be laid down in writing.

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.

It is acknowledged that, in the case of ATMPs, out of specification products are not always attributable to failures in the manufacturing process *(e.g.* idiopathic factors of the patient). All instances of out of specification products should be investigated and, where a failure in the manufacturing process is identified, the relevant corrective and/or preventive actions taken to prevent recurrence documented. In case of recurrent deviations, the need for changes to the manufacturing process should be assessed.

11.3.3. Batch release process in cases of decentralised manufacturing:

The manufacturing process is key for the quality, as well as the safety and efficacy attributes of ATMPs and it is therefore particularly important to ensure that the manufacturing process and control methods applied are in accordance with the marketing/clinical trial authorisation and that GMP is respected. The process of batch certification and batch release, as well as the role of the QP is an essential step in this regard.

There may be cases where manufacturing of the ATMP needs to take place in sites close to the patient (*e.g.* ATMPs with short shelf-life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, *etc*.). In such cases, manufacturing of the ATMPs may need to be decentralised to multiple sites so as to reach to patients across the EU ("decentralised manufacturing"). This scenario may occur both in the context of authorised ATMPs as well as in the context of investigational ATMPs.

The batch certification and release process becomes particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and checked in accordance with the requirements of the marketing authorisation/clinical trial authorisation and other relevant regulatory requirements including compliance with GMP. To this effect, the following aspects need to be considered:

(i) A "central site", which should be established in the EU, should be identified. The central site is responsible for the oversight of the decentralised sites. To this end, the central site assumes, as a minimum, the following tasks:

- ensuring that those involved in the batch certification and release process are adequately qualified and trained for their tasks, and

- performing audits to confirm that the batch certification and release process (as descripted in SOP) is complied with.

The marketing authorisation holder/sponsor may be the central site in cases when the marketing authorisation holder/sponsor also assumes the role of manufacturer.

(ii) There should be a written contract/technical agreement between the central site and the decentralised sites establishing the responsibilities of each party, including the responsibility of the QP.

(iii) The steps of the batch certification and release process should be laid down in writing (SOP). The responsibilities of each of the sites/actors involved should be clearly explained. There should be no gaps or unexplained overlaps in the responsibilities of the personnel concerned. The process should also be explained, as appropriate, in the context of the marketing authorisation application/clinical trial authorisation.

(iv) A QP established in the EU should have ultimately responsibility for the batch certification. However, it should be possible for the QP of the central site to rely on data/information that is transmitted to him by qualified and trained personnel at the decentralised sites.

(v) If a deviation occurs at the decentralised sites, it should be approved in writing by a responsible person (after having assessed the impact thereof on quality, safety

and efficacy), with the involvement of the QP as appropriate. Deviations should be investigated with a view to identify the root cause and to implement corrective and preventive measures as appropriate. Any instances of quality defects, deviations or non-conformity should be immediately reported to the central site.

11.4. Handling of unplanned deviations

As long as the specifications for the finished product 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.

11.5. Administration of out of specification products

In cases where, for imperative reasons linked to the health of the patient (ATMP for a life-threatening condition which is either autologous or has been manufactured from materials of a matched donor), an out of specification product needs to be administered to the patient, the manufacturer should provide the treating physician with its evaluation of the risks (the possibility of reprocessing may be considered as appropriate). The agreement of the treating physician to use the product should be recorded by the manufacturer.

In addition to the above, when the out of specification product is administered to a trial subject, the impact of the use of an out-of-specification product in the clinical trial should be determined and notified to the sponsor. Instances of administration of an out-of-specification product to a clinical trial subject should be notified as soon as possible to the relevant competent authorities.

12. Quality control

12.1. General principles

Quality control ("QC") is intended to 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 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, medical devices that are used in combined ATMPs, packaging materials, intermediate, bulk and finished products (including approval or rejection thereof). In case of autologous products or allogeneic products in a donor-match scenario, the match between the origin of the starting material and the recipient should be verified (information on the origin of the cells/tissues should be checked).

Where, exceptionally, there is release of expired materials for use in the manufacturing process, the person responsible for quality control should ensure the quality thereof through appropriate retesting.

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

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

(vi) Ensuring the monitoring of the stability of the products.

(vii) Participation in investigations 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 (vi).

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.* description of procedures or records from the manufacturing process and testing) should also be accessible.

12.2. Sampling

12.2.1. General principles

Samples should be representative of the batch of materials or products from which they are taken. Bulk containers from which samples have been drawn should be identified. In case of samples of sterile materials or samples that are taken during processing activities, identification of the sample should be done by other appropriate means.

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. When containers are too small, the use of bar-codes or other means that permit access to this information should be considered.

12.2.2. Retention of samples

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 sample of a fully packaged unit from a batch of finished product). The reference sample and the retention sample may be identical in some cases (*i.e.* a fully packaged unit).

As a general principle, a reference sample should be of sufficient size to permit the carrying out on at least two occasions of the full analytical controls on the batch foreseen in the marketing authorisation/clinical trial authorisation. However, it is acknowledged that this may not always be feasible due to scarcity of the materials or limited size of the batches (*e.g.* autologous products, allogeneic products in a matched donor scenario, products for ultra-rare diseases, products for use in first-in-man clinical trial with a very small scale production).

The retention sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

Samples should normally be stored under the conditions foreseen in the product information. However, for products/materials with a short shelf-life, it should be carefully considered if other storage conditions that maximise stability can be used (*see* below).

The sampling plan should be documented. The sampling plan should be adapted to the specific characteristics of the product. In designing the sampling strategy, the manufacturer should take into account the risks, the practical limitations that may exist, and possible mitigation measures (*e.g.* increased reliance on in-process testing). The sampling strategy of the manufacturer should be duly justified.

In particular, the following considerations apply:

- Samples of raw materials: Reference samples of critical raw materials (*e.g.* cytokines, growth factors, enzymes, sera) are important to investigate possible quality problems with the product. The assessment whether a specific raw materials is critical should be done by the manufacturer (or, as appropriate, by the sponsor or marketing authorisation holder) having regard to the specific risks and possible mitigation measures (*e.g.* increased QC controls). The decisions taken should be documented. Samples of critical raw materials should be retained during the shelf-life of the relevant raw materials.

- Samples of the starting materials should generally be kept for two years after the batch release. However, it is acknowledged that the retention of samples may be challenging due to scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep reference samples of the cells/tissues used as starting materials in the case of autologous ATMPs and certain allogeneic ATMPs (matched donor scenario). In other cases where the scarcity of the materials is also a concern, the sampling strategy may

be adapted provided that this is justified and appropriate mitigation measures are implemented.

- Samples of active substances and intermediate products should generally be kept for two years after the batch release. However, it is acknowledged that for ATMPs it is not always possible to separate the sampling of the starting materials, active substance, intermediate and finished product. The considerations regarding scarcity of starting materials apply -adapted as necessary- to the expectations on the retention of samples of active substances and intermediate products.

- Samples of primary packaging material: Samples of primary packaging material should generally be retained for the duration of the shelf-life of the finished product concerned. The retention of samples of primary packaging material may not be necessary in certain cases, having regard to the risks of the materials and/or other relevant consideration (*e.g.* increased QC controls, primary packaging material is certified as a medical device). A decision not to keep samples of primary packaging materials should be duly justified and documented.

- A sample of a fully packaged unit (retention sample) should be kept per batch for at least one year after the expiry date. A retention sample is, however, not expected in the case of autologous products or allogeneic products in a matched donor scenario as the unit produced with the patient's tissues/cells constitutes should be administered to the patient. When it is not possible to keep a retention sample, photographs or copies of the label are acceptable for inclusion in the batch records.

The retention period of samples of starting materials, active substance and intermediate product should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be justified. In cases of short shelf-life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf-life (such as cryoprervation) is representative for the intended purpose. For instance, cryoprervation of fresh-cells may render the sample inadequate for characterisation purposes but the sample may be adequate for sterility or viral safety controls (the volume of the samples can be reduced according to the intended purpose). When the cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches (*e.g.* sample of intermediate product such as differentiated cells.)

12.3. Testing

Testing is important to ensure that each batch meets the relevant specifications. 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.

Testing of critical raw materials, starting materials, 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 validated and reference materials should be established (where available) for qualification and routine testing. For investigational ATMPs, the level of validation should be commensurate with the development phase and the criticality of the test results considering the risks for the patient (*see* Section 10.4).

The following records should be kept in connection with the tests performed:

(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 (or another suitable identification system).

(vii) Initials of the persons who verified the testing and the calculations, where appropriate (or another suitable identification system).

(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.

Materials, reagents, culture media and reference standards used for QC tests should be of appropriate quality and used according to instructions. Where necessary, identity verification and/or testing should be considered upon receipt or before use.

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 any 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. On-going stability program

After the marketing authorisation is granted, a program should be implemented to verify that, under the relevant storage conditions (as foreseen in the marketing authorisation), the product remains within the specifications during the shelf-life (so called- "on-going stability program"). The methodology in the on-going stability programme can differ from the approach followed to obtain the stability data submitted in the marketing authorisation application (*e.g.* different frequency of testing), provided that it is justified.

The on-going stability studies should generally be performed on the finished product (*i.e.* as released by the manufacturer). When intermediates can be stored for extended periods of time, consideration should be given to include in the stability program those batches that have been manufactured from materials stored for longer periods of time. Stability studies on the reconstituted product are performed during product development and need not be monitored on an on-going basis. The use of surrogate materials (*i.e.* material derived from healthy volunteers) is acceptable in case of autologous products (or matched donor scenario) where the batch needs to be administered in its entirety to the patient.

The number of batches and frequency of testing should be adequate to allow for trend analysis. It is generally expected that at least one batch of the product is included per year in the stability program, unless none are produced in a given year or a different frequency is otherwise justified. Out of specifications and significant atypical trends should be investigated and their possible impact on the batches on the market should be assessed and reported to the competent authorities as appropriate.

13. Outsourced activities

13.1. General principles

Activities that are outsourced to a third party (including consultancy work) should be governed by a written contract that establishes the responsibilities of each party. As appropriate, the role and responsibilities in the event of detection of quality defects should be clearly established in the contract, as well as –where applicable- the obligations of each party regarding traceability.

13.2. Obligations of the contract giver

Prior to outsourcing any activity, the manufacturer, or – as appropriate- the sponsor or marketing authorisation holder ("contract giver") should assess the suitability of the contractor ("contract acceptor") to carry out the outsourced activities in accordance with the terms of the marketing authorisation/clinical trial authorisation and other applicable regulations, including compliance with GMP.

Exceptionally, when the outsourced activity is a highly specialised test (*e.g.* karyotype test), it is acceptable that the contract acceptor is not GMP-certified, provided that it complies with suitable quality standards relevant to the outsourced activity (*e.g.* ISO) and that this is duly justified.

The contract giver should provide the contract acceptor with detailed information on the product/manufacturing process, as well as any other data that is necessary to carry out the contracted operations correctly.

The contract giver should review and assess the records and the 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 outsourced 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 outsourced activity without the prior approval of the contract giver.

All records related to the outsourced activities as well as reference samples should either be transferred to the contract giver or, in the alternative, the contract giver should be granted access to them.

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

The contract acceptor should permit audits/inspections by the contract giver and the competent authorities in connection with the outsourced activities.

14. Quality defects and product recalls

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. Personnel responsible for managing complaint and quality defect investigations should be independent from marketing and sales departments unless otherwise justified. If the QP involved in the certification of the concerned batch(es) does not participate in the investigation, it should be informed in a timely manner.

Operating procedures should be developed describing the actions to be taken upon the receipt of a complaint, addressing in particular the identification of the potential root cause(s) of the quality defect, the assessment of the risk(s) posed by the quality defect, the need for appropriate corrective or preventive measures, the assessment of the impact that any recall action may have on the availability of the medicinal product to patients, and the internal and

external communications that should be made. Where the root cause cannot be ascertained, the most probable reasons should be identified.

If additional donor (human or animal) health information becomes available after procurement, which affects product quality, an analysis of the risk(s) and of the need for corrective or prevented measures is also required.

When 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-management measures are taken to ensure patients safety. All decisions and measures adopted should be documented. The effectiveness of the corrective and/or preventive measures implemented should be monitored.

Quality defect records should be retained and used to evaluate the possible existence of recurring problems. Competent authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with an ATMP which may result in the recall of the product or an abnormal restriction in the supply. Unplanned deviations as described in Section 11.4 should not be notified.

Where the ATMP is manufactured by an entity that is not the marketing authorisation holder/sponsor, the role and responsibilities of the manufacturer, the marketing authorisation holder/sponsor and any other relevant third parties in relation to assessment, decision-making, dissemination of information, and implementation of risk-reducing actions should be laid down in writing.

<u>Additional considerations for investigational ATMPs</u>

Where blinding of investigational medicinal products is required by the protocol of a clinical trial, the manufacturer should implement a procedure for the rapid unblinding of blinded products where this is necessary for a prompt recall. The manufacturer should ensure that the procedure discloses the identity of the blinded product only in so far as it is necessary.

14.2. Product recalls and other risk-reducing actions.

Measures to address quality defects should be proportionate to the risks and the priority should be the protection of patients. Whenever possible, the actions to be taken should be discussed with the concerned competent authorities in advance.

There should be established written procedures for the recall of products, including how a recall should be initiated, who should be informed in the event of a recall (including relevant

authorities and clinical sites), and how the recalled material should be treated. The procedure should foresee the reconciliation between the delivered and the recovered quantities and the recording of the progress until closure. The documented destruction of a defective product at the clinical site is an acceptable alternative to the return of the product. Recalled products should be clearly identified and segregated.

It should be ensured that recall operations can be initiated promptly and at any time. In certain cases and with a view to protect public health, it may be necessary to recall products prior to establishing the root cause or the full extent of the quality defect.

In order to test the robustness of the recall procedure, in the case of authorised ATMPs, consideration should be given to the possibility of performing mock-recall actions. However, it is acknowledged that a mock-recall action may not be appropriate in certain settings (*e.g.* autologous ATMPs, allogeneic ATMPs in a matched donor scenario, ATMPs where the time between manufacturing and administration of the product to the patient is very short).

All concerned competent authorities should be informed prior to the initiation of a recall operation unless urgent action is required to protect public health.

An action plan should be established for cases where the product cannot be recalled because it has already been administered to the patient(s). In addition to recalls, there are other risk-reducing actions that may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals.

15. Environmental control measures for ATMPs containing or consisting of GMOs

The handling of ATMPs containing or consisting of GMOs may pose a risk for the environment, requiring the implementation of additional control measures. As a first step, an assessment of the risks should be performed taking into account the risk of the isolated ATMP, as well as the risk in case of expansion inside a permissive cell host. The risk assessment should result in a categorization of the products as having a negligible, low, moderate or high risk for the environment.

Containment measures should be established according to the risk of the product that is handled, including measures regarding the design of the premises, organizational and technical measures, and measures regarding the treatment of residues.

Where replication limited viral vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors. The handling of viral vectors should take place in a segregated area and in a biological safety cabinet or an isolator.

Appropriate decontamination measures should be implemented when personnel or materials move from an area containing GMOs to an area not containing GMOs or between areas containing different GMOs. Unidirectional flows should be considered where possible.

Emergency plans (adapted to the level of risk) should also be in place covering the actions to be taken in case of accidental release into the environment. The plan should foresee measures/procedures for containment, protection of personnel, cleaning, decontamination, waste management, as well as the notification to the local competent authorities and, where appropriate, the emergency services.

In the case of authorised ATMPs, the risk assessment, the containment measures and the emergency plan(s) should be part of the Risk Management Plan. In the case of investigational ATMPs, the suitability of the containment measures and the emergency plan(s) is assessed as part of the authorisation by the competent authorities responsible for GMOs.

16. Reconstitution of product after batch release

16.1. Reconstitution activities

Reconstitution activities can be performed at the administration site *(e.g.* in hospital pharmacies) outside a GMP environment.

For the purposes of these Guidelines, the term "reconstitution" covers activities required after batch release and prior to the administration of the ATMP to the patient, and which cannot be considered as a manufacturing step.[23] No activity that entails substantial manipulation can, however, be considered reconstitution (*e.g.* cultivation). Substantial manipulations should be conducted under GMP.

The following are examples of reconstitution activities relevant for ATMPs. It is stressed that these examples cannot be extrapolated to medicinal products other than ATMPs:

- Thawing, washing, buffer exchange, centrifugation steps necessary to remove preservation solution (*e.g.* DMSO), removal of process related impurities (residual amount of preservation solution, dead cells) including filtering.

- (Re)suspension, dissolution or dilution with solvent/buffer, dispersion.

- Mixing the product with patient's own cells, with an adjuvant and/or with other substances added for the purposes of administration (including matrixes). However, the mixing of a gene therapy vector with autologous cells is a manufacturing activity that should be conducted under GMP.

- Splitting the product and use in separate doses, adaptation of dose (*e.g.* cell count).

- Loading into delivery systems/surgical devices, transfer to an infusion bag/syringe.

The above steps can only be part of the reconstitution process if it is appropriately justified that these steps cannot be performed as part of the manufacturing process before batch release without negative impact on the product. Additionally, the above activities can only be

[23] Grinding and shaping are part of surgical procedures and therefore are neither manufacturing, nor reconstitution activities.

considered "reconstitution" when they are carried out at administration site (*i.e.*it is not acceptable to have these steps outsourced to a third party that is not GMP-compliant).

16.2. Obligations of the ATMP manufacturer in connection with reconstitution activities.

The manufacturer should validate the reconstitution processes to be followed from the point of batch release to the moment of administration to the patient; *i.e.* through appropriate studies it should be demonstrated that the specified reconstitution process is sufficiently robust and consistent so that the product can be administrated without negative impact on quality/safety/efficacy profile of the ATMP.

The manufacturer, or –as appropriate- the sponsor or marketing authorisation holder- should describe the reconstitution process, including equipment to be used and requirements at the site of administration. The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product (*e.g.* when the reconstitution involves thawing, the waiting period at room temperature, the rate of temperature change during thawing, use of water bath, *etc.* should be described).

Likewise, when the reconstitution requires the use of solvents and/or other materials these should be specified or, as appropriate, provided.

The compliance of the administration site with the defined reconstitution process falls outside the responsibility of the manufacturer and is also outside the scope of GMP.

17. Automated production of ATMPs

17.1. General principles

If the output of an automated production system (hereafter referred to as "automated equipment") meets the definition of ATMP (either because the process amounts to substantial manipulation of the cells/tissues, or because the cells/tissues are used for a different essential function in the recipient as in the donor), the requirements of the Regulation (EU) No 1394/2007 apply. Therefore, in the case of authorised ATMPs or ATMPs used in a clinical trial setting, GMP requirements (as laid down in these Guidelines) apply.

The use of functionally closed manufacturing equipment may, however, ease compliance with certain GMP requirements and may also bring certain advantages in respect to product's quality. This Section outlines some specific aspects relevant to the use of this technology for the manufacture of ATMPs but, unless stated otherwise, the remaining Sections of these Guidelines are also applicable.

17.2. Automated equipment

The ATMP manufacturer is responsible for the quality of the ATMP and, therefore, has to ensure the suitability of the automated equipment for the specific intended purpose.

While the level of effort to demonstrate suitability may be reduced when the automated equipment is certified for the intended used according to the EU medical device legislation

(CE mark), it is stressed that the CE mark may not be relevant (*i.e.* automated equipment that does not qualify as medical device) and that, in any case, the CE mark does not suffice to demonstrate suitability as required for under these Guidelines.

Of particular relevance are the following obligations of the ATMP manufacturer:

- Qualification of the equipment: The qualification process as described in Section 10.1 applies. The user requirement specifications should be clear, unambiguous and detailed enough to ensure the suitability of the automated equipment for the intended operations.

  In turn, the amount of information received from the manufacturer of the automated equipment should be sufficient for the ATMP manufacturer to fully understand the functioning of the automated equipment and to identify the steps critical for the quality, safety and efficacy of the product. Additional tests and operating procedures should be developed by the ATMP manufacturer where appropriate (*e.g.* in case of information gaps in the information provided by the manufacturer of the automated equipment, or deviations from the operating instructions supplied).

  The automated equipment should not be used outside the recommendations of its manufacturer/supplier, unless the new operating mode has been fully validated.

- Standard operating procedures should be developed. SOPs should be clear and detailed enough to ensure that the operators understand the manufacturing process and the associated risks. SOPs should also ensure that any deviation can be rapidly identified and that appropriate measures are taken.

- Adequate maintenance: Maintenance of the automated equipment to ensure optimal conditions of use and to avoid unintended deviations/instances of malfunctioning is essential.

  A program of services/calibration at regular intervals required to ensure the good performance of the automated equipment should be described by the manufacturer thereof. In turn, the ATMP manufacturer should ensure that the maintenance program is performed. As appropriate, the split of responsibilities between the manufacturer of the automated equipment and the manufacturer of ATMPs should be laid down in writing.

- Aseptic processing: The automated equipment should only be used under conditions that ensure aseptic processing (*e.g.* validation of cleaning processes, sterilisation of multiple-use materials that are in contact with the product, adequate checks of the integrity of the equipment, for example, by means of pressure-hold test or leak testing, *etc*.).

- Batch and traceability records should be kept.

17.3. Personnel

Personnel involved in production should be adequately trained and the associated risks of the process should be duly understood (including risks to the efficacy of the product).

17.4. Premises

As explained in Section 9.5.1, the room where a closed system is used should be of at least grade D. The transfer of the material into/from the equipment is a critical step and a validated procedure should be put in place to preserve the product from the risk of contamination.

Section 9.5.1 also explains the conditions under which, exceptionally, closed systems may be placed in a controlled but non-classified environment.

17.5. Production and process validation

The definition of the moment when the manufacturing process starts and finishes should be defined and the role and responsibilities of all actors involved at the different time-points should be clearly established.

Possibilities for in-process controls may be limited by the continuous closed processing. In such cases, continuous monitoring of critical process parameters and other input parameters that affect product quality (as identified in the marketing authorisation/clinical trial authorisation) should be performed if technically possible. When continuous monitoring is not technically possible, monitoring at appropriate intervals having regard to the criticality of the parameter and the risks is required. Data on process parameters should be kept as part of the batch records.

Validation of aseptic processing by media fill simulation should also be performed. The bi-annual frequency is recommended but it could be adapted having regard to the risks (*see* Section 9.5.2).

17.6. Qualified Person and Batch Certification

Batch certification is a fundamental requirement for all medicinal products, including ATMPs that are manufactured using automated equipment.

Glossary

1. Animals

- ***Founder animal:*** animals from which the source/donor animals are initially bred.

- ***Specified pathogen free (SPF):*** Animal materials (*e.g.* chicken embryos or cell cultures) used for the production or quality control of ATMPs, which are derived from groups (*e.g.* flocks or herds) of animals free from specified pathogens. Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

2. Air-lock: An enclosed space with two or more doors, and which is interposed between two or more rooms, *e.g.* of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

3. Area: An "area" is a space. A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air handling unit is considered as a single area.

- ***Clean area*****:** An area designed, maintained, and controlled to prevent particle and microbiological contamination.

  - *Critical clean area*: an area where the product is exposed to environmental conditions.

  - *Background clean area*: environment in the immediate vicinity of the critical clean area.

- ***Contained area*****:** An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

- ***Segregated area:*** a segregated area within a manufacturing site requires separate cryostorage, separate production suite with separate HVAC, restrictions on the movement of personnel and equipment (without appropriate decontamination measures) and dedicated equipment reserved solely for the production of one type of product with a specific risk profile.

4. Bulk Product: any product which has completed all processing stages up to, but not including, final packaging.

5. Campaigned manufacture: The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to pre-

established control measures before transfer to another product. Use of the same equipment for distinct products is possible provided that appropriate control measures are applied.

6. Cell bank

- ***Cell bank system:*** A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank. A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

- ***Master cell bank:*** A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. The master cell back is used to derive all working cell banks.

- ***Working cell bank:*** A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures.

7. Cell stock: primary cells expanded to a given number of cells to be aliquoted and used as starting material for production of a limited number of lots of a cell-based ATMP.

8. Clean room: A room designed, maintained, and controlled to prevent particle and microbiological contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

9. Cleaning validation: *See* Section 10.2

10. Cleaning verification: the gathering of evidence through appropriate analysis after each batch/campaign to show that contaminants, residues of the previous product or cleaning agents have been reduced below a pre-defined threshold.

11. Closed system: A process system designed and operated so as to avoid exposure of the product or material to the room environment. Materials may be introduced to a closed system, but the addition must be done in such a way so as to avoid exposure of the product to the room environment (*e.g.* by means of aseptic connectors or fusion systems).

A closed system may need to be opened (*e.g.*, to install a filter or make a connection), but it is returned to a closed state through a sanitization or sterilization step prior to process use.

12. Isolator: A decontaminated unit supplied with grade A (ISO 5) or higher air quality that provides uncompromised, continuous isolation of its interior from the external

environment (*i.e.*, surrounding cleanroom air and personnel). There are two major types of isolators:

- ***Closed isolator systems*** exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

- ***Open isolator systems*** are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (*e.g.*, using continuous overpressure) to exclude the entry of external contamination into the isolator.

13. **Intermediate:** Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

14. **Manufacturing order**: document that contains the request of the sponsor to manufacture a given product. The document should be unambiguous and it should refer to the product specification file and the relevant clinical trial protocol as appropriate. As the product specification file is typically subject to changes, particular attention should be paid to the identification of the version that the manufacturer should adhere to.

15. **Product Specification File:** a file containing, or referring to files containing, the specifications, instructions and other information necessary for the manufacturing of an investigational medicinal product and to perform batch certification. The specific content thereof is explained in Section 6.2.

16. **Qualification of premises and equipment:** *see* Section 10.1.

17. **Qualification of suppliers:** Process designed to ensure the suitability of suppliers. Qualification of suppliers may be done through various means, *e.g.* by means of quality questionnaires, audits, *etc*).

18. **Raw materials**: The definition of "raw materials" is provided for in Part IV of the Annex to Directive 2001/83/EC on the Community code relating to medicinal products for human use.

19. **Room status:**

- ***At rest:*** "At rest" state is the condition where all HVAC systems and installations are functioning but without personnel and with equipment static. The particle limits should be achieved after a short "clean up period" of approximately 15-20 minutes after completion of operations.

- ***In operation*:** "in operation" state is the condition when all equipment and installations are functioning and personnel are working in accordance with the manufacturing procedure.

20. Seed lot

- ***Seed lot system*:** A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than what has been shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

- ***Master seed lot***: A culture of a micro-organism (virus or bacteria) distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability.

- ***Working seed lot***: A culture of a micro-organism (virus or bacteria) derived from the master seed lot and intended for use in production.

21. Substantial manipulation: The criteria of substantial manipulation is laid down in Article 2(1) of 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). Additional guidance on the application thereof can be found in the CAT Reflection paper on classification of advanced therapy medicinal products (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp).

22. Starting materials: The definition of ”starting materials” is provided for in Part IV of the Annex to Directive 2001/83/EC on the Community code relating to medicinal products for human use.