Consultation Document

Good Manufacturing Practice for Advanced Therapy Medicinal Products

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

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

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1. Introduction

Quality plays a major role in the safety and efficacy profile of ATMPs. It is the responsibility of the ATMP manufacturer to ensure that the manufacturing process is adequate and that appropriate measures are put in place to safeguard the quality of the product (so-called "pharmaceutical quality system"). Senior management should be actively involved to ensure the effectiveness of the pharmaceutical quality system.

Compliance with Good Manufacturing Practice ("GMP") is an essential part of the pharmaceutical quality system. The main objectives of GMP are that:

- the personnel is 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, and the identification of any process deviation as well as the implementation of appropriate corrective action(s);
- there is a quality control system which is operationally independent from production;
- quality defects are identified as soon as possible, the causes investigated, and appropriate measures are taken,
- adequate systems are implemented to ensure traceability of the ATMPs and its starting and raw materials.

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

These Guidelines develops the GMP that should be applied in the manufacturing of advanced therapy medicinal products in the EU (including advanced therapy investigational medicinal products). 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 recalled, however, that non-substantial amendments can be introduced in the investigational medicinal product dossier without the agreement of the competent authorities.[1] Throughout this document, the term "clinical trial authorisation" should be understood as including also non-substantial amendments that have been made to the investigational medicinal product dossier.

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 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 allogenic 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.

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

The possibility for the manufacturer to apply alternative, more flexible approaches is particularly important in the case of investigational ATMPs, specially in early phases of clinical trials (phase I and phaseI/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). 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.

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

[1]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).

2.2 Application of the risk-based approach by ATMP manufacturers

Manufacturers are responsible for the quality of the ATMPs they produce. The risk-based approach ("RBA") 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 additional measures, if that is necessary to address the specific risks of the product or the manufacturing process.

The quality risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells, the biological characteristics of the vectors, 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. The manufacturing process, including in-process testing and batch release testing, should be adequate to address the identified risks.

When identifying the control 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. The level of effort and documentation should be commensurate with the level of risk.

Investigational ATMPs

The safety of the product needs to be ensured from the first stages of development. Nevertheless, it is acknowleged 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 additional waivers/flexibilities may be possible in early phases of clinical trials (phase I and I/II), 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 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 strongly 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 description of the manufacturing process and process controls in the clinical trial authorisation application should also describe, 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.

Authorised ATMPs

For authorised ATMPs, the starting point for the application of the risk-based approach is 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 flexibility/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 shoud 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.

2.3 Examples of the application of the risk-based approach

This section contains a non-exaustive list of examples to illustrate some of the possibilities and limitations of the risk-based approach ("RBA").

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 material 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.* basic media vs. growth factors), or the use thereof in the manufacturing process (higher risk if the raw material is in direct contact with the starting materials).

Finally, it needs to be assessed if the control strategy (*i.e.* qualification of suppliers) 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 posible to perform the release tests on the combined components of certain combined products, time restrictions (*i.e.* the product needs to be administered inmediatly 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 (and, as appropriate, be explained in the marketing authorisation/clinical trials authorisation application) based on the validation of the manufacturing process and the in-process controls. For example, consideration can be given to the following options:

- Testing of 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 finished product can be demonstrated.

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

The following examples may also be considered:

- The application of the sterility test to the final product in accordance with the European Pharmacopoeia (Chapter 2.6.27) 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 (*e.g*. use of alternative methods for preliminary results, combined with sterility testing of media or intermediate product at subsequent (relevant) time points, *etc.*). If the results of the sterility test of the product are not available at release, appropriate mitigation measures should be implemented, including information of the treating physician (*see* Section 11.3.2).

- As cells in suspension are not clear solutions, it is acceptable to limit the particulate matter test to foreign visible particles, provided that alternative measures are put in place such as controls of input of particles from materials 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 a very short shelf-life.

2.3.3. Additional considerations specifically relevant for ATMPs that are not subject to substantial manipulation[2]

The manufacturing process of ATMPs which does not involve substantial manipulation of the cells/tissues is typically associated with lower risks than the manufacturing of ATMPs that

[2] 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).

require 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 avoid unnecessary 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[3] or for research purposes should be validated in accordance with these Guidelines.

It is stressed that it is the responsibility of the manufacturer to ensure that the manufacturing of ATMPs is done under aseptic conditions, also when the manufacturing process does not involve substantial manipulation. When manufacturing operations take place in an open environment in premises other than a critical room of grade A in a background clean area of grade B, a risk-analysis study should be conducted (particular consideration should be paid to the time that the product is exposed to the environment) and it should be demonstrated that the implemented control measures are adequate to ensure aseptic manufacturing. Under no circumstances it is acceptable to conduct manufacturing operations in premises with air quality classification lower than a critical clean room of grade A in a background clean area of grade D.

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 product characterisation, process validation and quality controls as required for in these Guidelines are critical to ensure that the ATMP administered to the patient is the one that has been authorised. Additionally, in a clinical trial setting, lack of appropriate product characterisation and adequate quality controls may affect the reliability of the results of the clinical trial. Moreover, QP release is an essential requirement applicable to all medicinal products, including authorised and investigational ATMPs the manufacturing of which does not involve substantial manipulation.

[3] 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).

2.3.4. Additional considerations specifically relevant for investigational ATMPs

The application of GMP requires certain level of flexibility in the case of investigational ATMPs. However, the quality of the product should be ensured, also in an investigational setting. Accordingly, particular attention should be paid to personnel training (in particular on aseptic manufacturing), ensuring conditions for aseptic manufacturing, and equipment calibration.

The following are examples of the additional flexibilities that are acceptable in the case of investigational ATMPs:

- For first-in-man clinical trials, production in an open environment may be performed in a critical clean area of grade A in a background clean area of grade C if appropriate controls of microbiological contamination, separation of processing procedures, and validated cleaning and disinfection 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.

- In early phases of clinical research (clinical trial phases I/II) when the manufacturing activity is very low, annual calibration, inspection or checking can be limited to the facility, cabinets, incubators, isolators, freezers, air sampler and particle counters, unless a lower frequency is justified due to periodicity of use. The rest of equipment could be tested less frequently based on a risk analysis and the production activity. The suitability for use of all equipment should be verified before it is used.

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

- During early phases of clinical development (phase I/II clinical trials) specifications can be based on wider acceptance criteria taking due account of the current knowledge of the risks.

- Additional flexibilities regarding qualification of premises and equipment, 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 be aware of 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 areas where contamination is a hazard should be given specific training on aseptic manufacturing. Prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test (*see* Section 9.5.3). Training in gowning requirements set out in section 3.3 is also required.

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

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 product from contamination.

The description of clothing required for each grade is as follows:

- Grade D: Hair and, where relevant, beard 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: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. 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 should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. 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, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, appropriate control measures (having regard to the risks) should be applied. When a person moves from one clean room to another clean room appropriate disinfection measures should be applied.

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. As far as possible, 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 should be 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.

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.

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, while the person responsible for quality control should take responsibility for the control of raw materials, starting materials, packaging materials, intermediate, bulk and finished products (including approval/rejection thereof).

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 QC and production activities, it is acceptable that the same person is responsible for both roles (production and quality control) with respect to different batches. In those cases, it becomes particularly important that the independency of the QC activities from the production activities for the same batch is clearly established through appropriate written procedures.

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) 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.

(f) 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. Production areas

4.2.1. Design and construction

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

If the manufacturing site produces medicinal products other than ATMPs, the manufacture of ATMPs should take place in a dedicated area of the facility. In the case of manufacturing of investigational ATMPs, it is accepted that the same area is used for multiple purposes, provided that appropriate cleaning and procedural controls are in place to ensure that there is no carry-over of materials or products, or mix-ups.

Segregated production areas (*see* Section 9.4(i)) should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. Specifically, manufacturing activities involving infectious viral vectors (*e.g.* oncolytic viruses) or materials from infected donors[4] should be done in a segregated area. The arrangements for the segregation of the area should be demonstrated to be effective. Closed systems should be used wherever possible.

In the case of investigational ATMPs, where there are no separate production suites, a thorough cleaning and decontamination procedure should take place before any subsequent manufacturing in the same area can occur.

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.

[4]Donors that have tested positively for HIV 1 and 2, Hepatitis B, Hepatitis C or Syphilis.

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

Production areas should be effectively ventilated, with air control systems (including temperature and, where necessary, humidity and filtration 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.

4.2.2. 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 to products for which there is no sterilisation of the finished product.

Clean areas

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 sterility. 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.

- Production in a closed system[5] or in an isolator: a background clean area of D grade 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, sanitisation 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

[5]A closed system ensures that, during the manufacturing process, the product is not exposed to the environment.

isolator is one of the greatest potential sources of contamination and appropriate control measures should be put in place.

- 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 (or similarly controlled environment) is required.

In the case of production in an open system, the following considerations apply:

- Preparation of solutions which are to be sterile filtered during the process can be done in a grade C environment.

- For the manufacturing process of viral vectors, two steps should be considered:
  - The expansion phase before the sterilizing filtration can be performed in a critical clean area of grade A with a background clean area of grade C.
  - The sterilizing filtration and filling need to be performed in a critical clean room of grade A with a background clean room of grade B.

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 both at rest[6] and in operation[7]. 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

[6] Room with all HVAC systems and installations functioning but without personnel and with equipment static. The particle limits should be measured after a short "clean up period" of approximatively 15-20 minutes after completion of operations.

[7] All equipment and installations are functioning and personnel is working in accordance with the manufacturing procedure.

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

Appropriate cleaning/sanitation of clean areas is essential. 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.

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.

4.2.3. Environmental monitoring

Environmental monitoring programs are an important part of the strategy to minimise the risk of contamination. The environmental monitoring program should include the following parameters: particulate matter/microbiological contamination, air pressure differentials, airflow direction, temperature and relative humidity.

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

Monitoring of clean rooms should be performed "in operation". Additionally, monitoring "at rest" should be performed as appropriate in order to identify potential incidents (*e.g.* prior to the start of manufacturing and post sanitization).

The number of samples and frequency of monitoring should be appropriate taking into account the risks and the overall control strategy.

Non-viable particulate monitoring

Airborne particle monitoring systems should be established to obtain data for assessing potential contamination risks and to ensure an aseptic environment. 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. 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.

The monitoring system should ensure that when alert limits are exceeded, the event is rapidly identified (*e.g.* alarm settings). The recommended action limits are as follows:

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
Grade	At rest		In operation	
	0.5 µm	**5.0µm**	**0.5 µm**	**5.0µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900

C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Limit to be set according to the risks.	Limit to be set according to the risks.

For Grade A zones, 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 risk). Monitoring should also be performed during simulated operations. The effectiveness of the segregation between the Grade A and B zones is an important consideration when designing the monitoring system of the grade B.

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.

When 'closed' systems are used for the manufacture of ATMPs, it may be justified not to conduct continued particle monitoring, for example when there is intrinsic particle generation by the process *(e.g.* spraying of disinfectants). A rationale for not utilising continuous particle monitoring should be documented, considering the risk to product and the source(s) of particles generated. Validation should demonstrate that in the absence of identified particle generating sources (such as spraying of sanitising agents under normal operating conditions), the Grade A zone will conform to the environmental requirements. A periodic monitoring exercise should demonstrate continued compliance with the requirements.

In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration 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 indicate 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 environment (*e.g.* host organism, yeast, moulds, anaerobes, *etc.*) should be performed as appropriate.

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 adapted after validation of the premises. Sampling methods used in operation should not interfere with zone protection.

The frequency of monitoring should be determined according to the contamination risks associated with the characteristics of the product and of the manufacturing process (*e.g.* in a closed production system the risk of contamination from operators can be reduced and therefore the frequency of monitoring can also be reduced).

Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, *e.g.* after validation of systems, cleaning and sanitisation.

The following recommended maximum limits for microbiological monitoring of clean areas apply (average values):

Grade	Air sample cfu/m3	Settle plates (diameter 90mm) cfu/4 hours*	Contact plates (diameter 55 mm)	Cfu plate glove print 5 fingers 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.

If these limits are exceeded, appropriate corrective actions should be taken. These should be documented.

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.

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

4.2.4. 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 Grade A/B should not have drains installed.

4.3. Storage areas

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

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

Where quarantine status is ensured by storage in separate areas, these areas 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 rejected, recalled or returned materials or products, unless control of these materials/products is ensured through electronic means.

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

4.4. Quality control areas

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

Quality control laboratories should normally be separated from production areas. 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.

4.5. Ancillary areas

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

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.

The integrity of the 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. Aseptic connections should be performed in a critical clean area of grade A with a background clean area of grade B.

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 shall 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 shall be maintained.

- Air vent filters should be hydrophobic and validated with integrity testing at appropriate intervals taking into account the specific risks.

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, preferably pre-sterilized/sterile. The cleaning/decontamination procedures applied to multi-use equipment coming into contact with the product should be validated (*see* 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.

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 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 or photographic media. 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.

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

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 appropriate and authorised persons and the date of entry into operation should be defined.

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 recalled that changes into the

manufacturing requirements approved as part of the marketing authorisation must be submitted to the competent authorities (variation procedure),[8] and that substantial modifications in the manufacturing process of an investigational ATMP require approval by the competent authorities.[9]

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). For raw materials of biological origin, the identification of the supplier and anatomical environment from which materials originate should also be described.
- For critical raw materials, quality requirements to ensure suitability for intended use, as well as acceptance criteria. Quality requirements agreed with suppliers should be kept (*see* Section 7.2).
- 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. Contracts and quality requirements agreed with the suppliers should be kept (*see* Section 7.3).
- Sampling and testing instructions (*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 and rejection criteria.

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

[8]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.

[9] 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.

(v) Specifications for other materials that are used in the manufacturing process and that can have a critical impact on quality, where appropriate (*e.g.* medical devices used in a combined ATMP).

(vi) Batch definition. For autologous products, each unit should be considered a distinct batch.

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

(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) 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 recalled that, for authorised ATMPs, the 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.[10]

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.

[10] *See* Article 11 of Regulation (EC) No. 1394/2007 on advanced therapy medicinal products.

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 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;
- 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 (*see* Section 12.3);
- the product yield obtained at relevant stages of manufacture;
- 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.
(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) Procedure for 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/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.[11]

6.5. Retention of documents

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 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.

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

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

The traceability of the cells/tissues contained in ATMPs should be ensured so that the donor of the cells and tissues used as starting materials can be identified, through the entire manufacturing process, storage and transport, up to the delivery of the finished product to the recipient.

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 develops 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) Donor identification code received from the tissue establishment/blood establishment. For cells and tissues that are not covered by Directive 2004/23 or Directive 2002/98[12], such as 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 donor identification code can always be established. For starting materials not covered by Directive 2004/23 or Directive 2002/98, 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

[12]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).

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 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 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.

7. Starting and raw materials[13]

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. 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 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).[14]

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.

Where 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

[13]The definition of "raw materials" and"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.

[14]Ph.Eur. chapter 2.6.12 on sterility testing describes the use of neutralising substances for products containing antibiotics.

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 manufacturer should ensure the suitability of such raw materials for the intended use, including –where appropriate– by means of testing (*e.g.* functional test). The ATMP manufacturer should put in place appropriate measures to ensure that raw materials can be traced in order to facilitate recall of products if necessary.

The ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder) should establish quality requirements for critical raw materials (specifications) which -where applicable- should be agreed with the supplier(s). The assessment whether a specific raw materials is critical should be done by the manufacturer having regard to the specific risks. The decisions taken should be documented. These specifications should cover aspects of the production, testing and control, and other aspects of handling and distribution as appropriate. The specifications set should be in compliance with the terms of the marketing authorisation or clinical trial authorisation.

The ATMP manufacturer should verify compliance of the supplier'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 (*e.g.* cytokines, human serum albumin, recombinant proteins) the certificate of analysis of the supplier is not required.

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 Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products is required. [15]

The risk of contamination from other raw 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.

Critical raw 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.

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

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/department responsible for quality control should be used.

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.[16] When the cells/tissues used are outside the scope of the Directive (*e.g.* cell-lines/cell banks established outside the EU, or cells procured before the entry into force of the Directive), the ATMP manufacturer 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 be agreed with the supplier(s). These specifications should cover aspects of the production, testing and control, and other aspects of handling and distribution as appropriate. Depending on the product's characteristics, testing in addition to that foreseen in the Directive 2004/23 may be required. 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. Blood establishments and tissue establishments authorised and supervised under Directive 2002/98 or Directive 2004/23 do not require additional audits by the ATMP manufacturer regarding compliance with the requirements on donation, procurement and testing.

In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting 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 viral and microbial safety and Transmissible Spongiform Encephalopathy ("TSE"). Compliance with the latest version of the Note for

[16] For blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing is likewise acceptable.

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/department responsible for quality control should be used.

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

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.

The initial processing steps of the starting materials (*e.g.* isolation, purification) are manufacturing activities that should be conducted in accordance with the manufacturing requirements for pharmaceuticals,[17] even if it is done by a third party (*e.g.* a tissue establishment). 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, even if the activities have been outsourced, and their release for use in the manufacturing process should be done by the QC 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.

<u>Additional considerations for xenogeneic cells and tissues</u>:

[17]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.

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)[18] and be raised in SPF conditions, including health monitoring. The donor/source animal 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[19] 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.

[18]Specific pathogen free means that the animals 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.
[19]Founder animals are the animals from which the source animals are initially bred.

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. 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 recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

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

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.

<u>Cell Stock</u>

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.

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.

The use of starting materials from cell stocks/cell banks and viral seed stocks generated (in the past) without full GMP in the manufacture of an ATMP 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 record 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. Significant changes, which may affect the quality, safety or efficacy of the product or the reproducibility of the process, should be assessed through a comparability study to assess the impact thereof on the quality profile of the product and, based on that, to evaluate the potential impact on the safety and efficacy of the product. 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 the person responsible for manufacturing, with the involvement of the person/department responsible for quality control when 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. 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 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[20] purchased as such should be released by the person/department 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.

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.

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

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 (*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/department 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). In the case of water for injection, special attention should be paid to prevention of microbial growth, for example by constant circulation at a temperature above 70˚C. Water for injection 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.

The use of pre-packaged water for injection compliant with the European Pharmacopeia removes the need for demonstrating the appropriateness of the quality of the water for injection as provided for in the previous paragraph.

9.3.2. Medical gases

Gasses that come into contact with the product during processing should be of suitable quality. Where possible, gasses compliant with the European Pharmacopoeia should be used.

Gasses taken into the aseptic work place or that come into contact with the product should be passed through micro-organism retentive filters.

9.3.3. Clean steam

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.

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.

At every stage of production, products and materials should be protected from microbial and other contamination. Mix-ups of materials should be prevented; special precautions should be taken to avoid the mixing of autologous materials or other dedicated materials. 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).

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 (*i.e.* 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.

(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. A risk-assessment should be used to determine the cleaning/decontamination procedures that are necessary, including the frequency thereof. For autologous products, there should be appropriate cleaning/decontamination between each batch. The cleaning/decontamination procedures should be validated (*see* 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 effectiveness of the measures implemented to avoid cross-contamination should be reviewed periodically according to set procedures.

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 sterilized. Therefore, 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) The premises should comply with the requirements in Section 4.2.2 and 4.2.3.

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

- Separation in place: "Closed systems" may be used to separate activities within the same room (each closed system is to be regarded as an area). Thus, the use of more than one isolator (or other closed systems) in the same room at the same time is acceptable, provided that there is separated expulsion of the exhausted air from the isolators and regular integrity checks of the isolator. Likewise, 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 isolator and regular integrity checks of the isolator.

  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.

  Concurrent manufacture of different viral vectors in the same area is also not acceptable. However, it is possible to use two isolators to process different viral vectors within the same room if appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials (*i.e.* regular integrity checks of the isolator; close, separate and unidirectional waste handling, separate expulsion of exhausted air from the isolators). Concurrent production of non-viral vectors in the same area is possible, provided that effective controls are put in place.

- 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.

(iii) 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 may be used.

Sterilisation of articles and materials elsewhere is acceptable provided that there are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitization precautions. Unless culture media is delivered ready-to-use (*i.e.* already sterilised by the supplier), it is recommended that media is sterilized 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). The effectiveness of the process should be checked at appropriate intervals.

(iv) 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 sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, etc. to bioreactors should be used where possible.

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. Sterilisation

The sterilization processes applied should be suitable having regard to the specific characteristics of the product. In particular, where sterilization of 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/reducing 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 sterilization method is not in accordance with the European Pharmacopoeia.

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 sterilised filter should be verified before use and should also be confirmed after use by an appropriate method (*e.g.* bubble point, diffusive flow or pressure hold test).

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.

9.5.3. Aseptic processing validation

The validation of aseptic processing should include a process simulation test using a nutrient medium (so-called "media fill"). A media fill process simulation is the performance of the manufacturing process using a sterile microbiological growth medium to test whether the manufacturing procedures are adequate to prevent contamination during production. Results and conclusions should be recorded.

If the validation of aseptic processing cannot be done by means of a media fill process simulation, an appropriate simulated model may be used, provided that this is duly justified.

The process simulation tests should follow as closely as possible the routine manufacturing process and it should be conducted in the same locations where the production occurs. However, alternative approaches may 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.

After the final product container is filled, it should be incubated for the time and under the temperature specified in the protocol/media fill procedure. All contaminants from the media fill 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.

Process simulation test should be performed as initial validation with three consecutive satisfactory simulation tests per shift.

It is generally expected that the process simulation test with media fill test is run every six months per shift, as well as when there is any significant change to the process *(e.g.* modification of HVAC system, equipment, *etc*). A reduced frequency in cases of infrequent production may be justified. Thus, 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 second batch (three consecutive runs should be performed).

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. A reduced frequency is not acceptable when the product should be administered to the patient prior to having the results of the sterility tests.

In case of manufacturing of various types of ATMPs, consideration can be given to the matrix approach (combined media fills for different ATMPs but based on identical handling of the product), provided that worse-case scenario is covered by the matrix approach.

9.6. Other operating principles

Critical process parameters and other input parameters that affect product quality (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 4.2.3) 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. 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 to EudraLex, Volume 4, should be consulted for further guidance.

9.7. Packaging

The suitability of primary packaging materials shall 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 for Phase I/II clinical trials may be more limited but it is expected that it becomes more detailed in later phases of development. For production of authorised ATMPs, selection, qualification, approval and maintenance of suppliers of primary packaging materials shall 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. 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 QC tests is addressed under Section 11.3.2.

9.9. Rejected, recovered and returned materials

Rejected materials should be clearly marked as such and stored separately in restricted areas. Starting and raw materials should either be returned to the suppliers or, 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[21] 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/department responsible for quality control. Records should be kept of the reprocessing.

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/department responsible for quality control.

[21] Article 54 of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

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, the manufacturer establishes 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 rooms should be qualified in accordance with ISO 14644-1 and re-qualified at appropriate intervals in accordance with ISO 14644-2.

- If computerized systems are used, their validation should be proportionate to the impact thereof on the quality of the product.

- For investigational ATMPs, it is expected that at least the suitability of the air quality system (in accordance with ISO 14644) 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 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.

Facilities and equipment should be re-evaluated at appropriate intervals to confirm that they remain suitable for the intended operations. Requalification should be done in accordance with ISO 14644-2. In general, for clean rooms of grade A, requalification is expected every six months, while for B, C and D grades requalification is expected on a yearly basis. A different frequency may, however, be justified in case of very small production.

10.1.2. Steps of the qualification process

The qualification strategy should follow the following steps:

(a) Setting the user requirement specifications: The manufacturer 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).

(b) Verifying compliance with the user requirement specifications: The manufacturer should verify that the premises/equipment comply with the user specifications. 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
- the materials of parts of the equipment that come into contact with the product are suitable.

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

(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 manufacturer 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.* information gaps exist having regard to the intended manufacturing process, equipment to be used differently than as intended by the manufacturer, *etc*.)

Where the qualification of the premises/equipment is outsourced to a third party, the principles laid down in Section 13 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 given 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 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 when designing the cleaning procedure.

- 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 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[22] 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).

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

(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. 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). 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.

Approach for investigational ATMPs

For investigational ATMPs, cleaning verification is acceptable when the volume of production is small (less than three batches). 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.

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 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 will 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 validation method, 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.

It is generally accepted that 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 1:1, 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 ration for the patient, a concurrent validation may be acceptable. The decision to carry out concurrent validation should be justified, having regard also to the possibility to use surrogate starting materials. 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 Qualified Person prior to the certification of the batch.

- Use of quality markers as an alternative to process validation: The process validation may be replaced by the continuous monitoring of surrogate markers reflecting critical quality attributes either as part of the control strategy (analogous to PAT) or the release process. This does not preclude the qualification of individual steps.

- Retrospective validation where time to manufacture, batch size, or other factors make prospective validation unethical *(e.g.* performing a biopsy only for validation purposes) or disproportionate having regard to the anticipated benefits for patients.

- Process validation for a class of products: where the same manufacturing process is used for a class of products (*i.e.* autologous T-cell based ATMPs), 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 the aseptic conditions of the manufacturing process have been validated.

Process validation/evaluation data should be collected throughout the development. It is recalled 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. Validation of test methods can follow a gradual approach during clinical development:

- Safety and microbial assay should be validated before first-in-man clinical trials.

- The suitability of analytical methods should be demonstrated for phase II and III clinical trials but a full validation report is not required.

- Potency assays should be validated throughout clinical development (*i.e.* typically validation finalized before phase III clinical trials).

Analytical procedures, which are either described in the European Pharmacopoeia, the pharmacopoeia of a Member State, USP or JP general chapter, or are linked to a product specific monograph, and are performed according to the monograph, are normally considered as validated.

11. Qualified person and batch release

11.1. General principles

Each manufacturing site in the EEA must have at least one Qualified Person ("QP").[23] 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 11.3.3, 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 or clinical trial authorisation,

- relevant regulations governing the manufacture of medicinal products, including GMP, and

[23] 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.

- relevant product specifications in the destination country (in the case of exports).

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 and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements applied in the EU.[24]

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.[25] However, it is acknowledged that for ATMPs it is not always possible to separate the testing of the active substance from the testing of the finished product. 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 under conditions equivalent to those applicable in the EU. The re-testing strategy should be in accordance with the terms of the marketing authorisation.

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

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

QPs should have access to:

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

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

<u>Relying on GMP assessments by third parties *e.g.* audits</u>

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 apply.

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

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

Involvement of more than one QP

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

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

Where more than one QP is involved 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.

11.3. Batch release

11.3.1. Batch release process

The process of batch release includes the following steps:

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

- all manufacturing steps (including controls and testing) have been done in accordance with the marketing authorisation or clinical trial authorisation,
- the specifications of 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 or clinical trial authorisation,
- 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 essential 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 or clinical trial authorisation.
- all required in-process controls and checks (including environmental monitoring) have been made and appropriate records exists,
- finished product quality control (QC) test data complies with the relevant specifications,

- on-going stability data continues to support certification,
- the impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete,
- all investigations related to the batch being certified has been completed and supports the certification of the batch,
- the self-inspection programme is active,
- appropriate arrangements for storage and transport exist,
- the presence of the safety features referred to in Article 54 of Directive 2001/83/EC have been verified, where applicable.[26]

It is acknowledged that, in the case of investigational ATMPs, the amount of relevant information 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 or clinical trial authorisation, and all other relevant regulatory requirements.

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

For investigational ATMPs, 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, whichever is the longest.

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

[26] 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).

afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or a contract.

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

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. Both steps should be documented.

Transfers of the investigational ATMPs from one trial side to another should remain the exception. When they occur, the QP is responsible to 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 preventive actions taken to prevent recurrence documented. In case of recurrent deviations, the need for changes to the manufacturing process should be assessed.

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, 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 to the relevant competent authorities.

12. Quality control

12.1. General principles

Quality control 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 donor-match situation, a control should be carried out to verify the match between the origin of the starting material and the recipient.

(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) Ensuring that the appropriate qualifications/validations are done.

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

(ix) 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 (viii).

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

12.2. Sampling

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.

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 samples of a fully packaged unit from a batch of finished product).

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 possible due to scarcity of the starting materials or limited size of the batches (*e.g.* autologous products, ATMPs for ultra-rare diseases).

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) 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 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 for two years after the batch release or one year after the expiry date of the relevant batch, whichever is the longest.

- Samples of the starting materials should generally be kept for two years after the batch release or one year after the expiry date of the relevant batch, whichever is the longest. 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).

- Samples of active substances and intermediate products should generally be kept for two years after the batch release or one year after the expiry date of the relevant batch, whichever is the longest. 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 based on an analysis of the risks and 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 reference samples and the retention sample may be identical in some cases (*i.e.* a fully packaged unit).

In all cases, the retention period 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 specification. In-process controls testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the product.

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 critically of the test results considering the risks for the patient (*see* Section 10.4).

The following records should be kept:

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

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

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

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

(v) Dates of testing.

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

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. No trending is however required in connection with an investigational ATMP.

Technical transfer of testing methods

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

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

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

(ii) Identification of 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. Stability monitoring 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 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 discussed with 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 the obligations of each party regarding traceability.

13.2. Obligations of the contract giver

Prior to outsourcing any activity, the manufacturer ("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.

When the outsourced activity is a highly specialised test (*e.g.* karyotype test), it is however acceptable that the contract acceptor does not operate under GMP, provided that it complies with suitable quality standards relevant to the outsourced activity (*e.g.* ISO or OCL).

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 contacted 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 be kept by, or made available to, the contract giver.

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

The contract acceptor should permit inspections by the contract giver 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, including 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, and the assessment of the impact that any recall action may have on the availability of the medicinal product to patients. 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-managements measures are taken to ensure patients safety. All decisions and measures adopted should be documented. The authorities should be informed in accordance with the relevant regulations.

The effectiveness of the corrective or preventive measures implemented should be monitored.

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

14.2. Product recalls

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

The documented destruction of a defective product at the clinical site is an acceptable alternative to the return of the product.

An action plan should be established for cases where the product cannot be recalled because it has already been administered to the patient(s).

15. Environmental control measures for ATMPs containing or consisting of GMO's

The handling of ATMPs containing or consisting of GMO's 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 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.

Emergency plans 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, and decontamination.

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.[27] 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.
- Cell recovery after cryo-storage.
- 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 into several aliquots and use in separate doses over a period of time, 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 QP release without negative impact on the product. Additionally, the above activities can only be 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

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

robust and consistent so that the product can be administrated without negative impact on quality/safety/efficacy profile of the ATMP.

The manufacturer should document 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 rate of temperature change during thawing should be described.)

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

17. Automated production of ATMPs

17.1. General principles

If the output of an automated production system 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. This means that the marketing of the ATMP requires authorisation by the European Commission, or by the national competent authorities in the context of the authorisation of the clinical trial or in application of the hospital exemption. Additionally, this also means that GMP requirements 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 user of the automated production system (hereafter referred to as "automated equipment" (*i.e.* 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:

- Validation of the equipment: The validation 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 should be described and the split of responsibilies of the manufacturer of the automated equipment and the responsibilities of the manufacturer of ATMPs should be laid down in writing.

- Asseptic processing: The automated equipment should be only used under conditions that ensure aseptic processing (*e.g.* validation of cleaning processes and sterilization of repeatedly used materials that are in contact with the product).

- 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 4, the room where a closed system is used should be of at least D grade. 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.

If justified having regard to the risks and provided that the approach is supported by validation data (*e.g.* leak testing and pressure check of the equipment), a controlled but non-classified background environment could be acceptable if the time between the donation and

administration of the material is very short and the manufacturing is performed at the operating room in the hospital (the patient is also in the operating room waiting for administration of the ATMP). The conditions of the operating room where the manufacturing activity takes place should be adequate and sufficient to ensure the quality and safety of the product.

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 and release controls are limited due to the continuous closed processing, limited amount of material and usually very short shelf-life. 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.

Lack of routine controls (due to continuous process in closed system and short shelf-life) of each individual batch must be compensated by a reinforced process validation.

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 9.5.3).

17.6. Qualified Person and Batch Release

Batch release is a fundamental requirement for all medicinal products, including ATMPs that are manufactured using automated equipment. Some specific elements described in Section may be considered in the context of automated production of ATMPs, such as the possibility that the same QP is responsible for more than one site, or the possibility to rely on audits conducted by third parties.