# ANNEX 2A

# MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

## SCOPE

The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, genome editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this annex. In a medicinal product, the genetically modified cells can be presented alone or combined with medical devices. This annex provides additional and specific guidance on the full range (as defined in the glossary) of ATMPs and the active substances that are used in their manufacture. Although one of the objectives of this present revision was to prepare a document that would stand for several years the field is quickly changing; it is recognised that amendments may be necessary to accommodate technological change, to clarify uncertainty or to specifically recognise important alternatives. Comments are therefore invited at any stage of the life of this edition. Interpretation and necessary adjustments will be given as Q&A until a new revision will be necessary.

This annex is divided into two main parts:

1) Part A contains supplementary guidance and alternative provisions on the manufacture of ATMPs, from control over seed lots and cell banks through to finishing activities and testing.

2) Part B contains further guidance on selected types of ATMPs and its substances.

This annex, along with several other annexes of the Guide to GMP, provides guidance which supplements that in Part I and in Part II of the PIC/S GMP Guide.

Table 1 gives examples of where this Annex applies. It should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that in line with the corresponding table, the level of GMP increases in detail from early to later steps in the manufacture of ATMPs active substances but should always adhere to GMP principles. The inclusion of some early steps of manufacture within the scope of this annex does not imply that those steps will be routinely subject to inspection by the authorities.

In certain cases, other national laws may be applicable to the starting materials for ATMPs. For example,

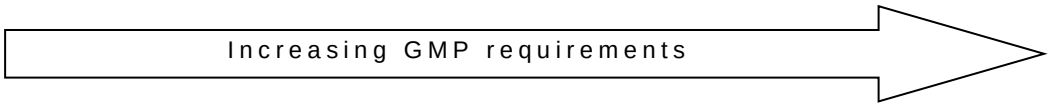
(a) Tissue and cells used as starting materials of ATMPs, donation, procurement, testing, processing, preservation, storage, and distribution of human tissue and cells may be covered by national law.

(b) Blood or blood components used as starting materials for ATMPs, national law may provide the technical requirements for the selection of donors and the collection and testing of blood and blood components[1].

Additionally, the manufacture and control of genetically modified organisms needs to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified micro-organism is handled. Advice should be obtained according to national law in order to establish and maintain the appropriate Biological Safety Level. There should be no conflicts with GMP requirements.

**Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2A**

| Type and source of material | Example product | Application of this guide to manufacturing steps shown in grey | | | |
|---|---|---|---|---|---|
| Human and/or animal sources | Gene therapy: genetically modified cells | Donation, procurement and testing of starting tissue / cells[1] | Vector manufacturing; cell isolation, culture and purification | Ex-vivo genetic modification of cells, Establishment of MCB, WCB or primary cell lot | Formulation, filling |
| | Somatic cell therapy | Donation, procurement and testing of starting tissue / cells[1] | Establishment of MCB, WCB or primary cell lot or cell pool | Cell isolation, culture, purification, combination with non-cellular components | Formulation, combination, fill |
| | Tissue engineered products | Donation, procurement and testing of starting tissue / cells[1] | Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool | Cell isolation, culture, purification, combination with non-cellular components | Formulation, combination, fill |
| Non-Human and/or animal sources | Gene Therapy: in Vivo Viral Vectors by stable producer cell lines | Plasmid manufacturing[1] | Producer cell lines manufacturing | Vector Manufacturing | Formulation, filling |
| | Gene Therapy: in Vivo Viral Vectors by transient production system | Virus manufacturing[1] | Cell system manufacturing | Vector Manufacturing | Formulation, filling |




See Glossary for explanation of acronyms.

# PRINCIPLE

The manufacture of ATMPs involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.

Since materials and processing conditions used in manufacturing processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, some

[1] Separate GMP requirements may apply where required under national law.

products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.

Specifications related to products (such as those in Pharmacopoeial monographs, Clinical Trial Authorisation (CTA), and Marketing Authorisation (MA) will dictate whether and to what stage ATMP substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the CTA or MA (e.g. number of generations (doublings, passages) between the seed lot or cell bank).

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of ATMP active substances and products.

# Part A: GENERAL GUIDANCE

Part A provides alternative or supplementary provisions to respective sections in Part I, II and annexes of the PIC/S GMP Guide, where necessary. Where this annex provides specific guidance for the manufacture of ATMPs, (including modification, replacement or redundancy of other sections) this will be clearly indicated. In the absence of specific guidance for ATMPs, compliance with other sections in the PIC/S GMP Guide is expected.

Note: Where the term Marketing Authorisation Holder (MAH) is used, unless otherwise specified, it should be intended to signify the “Sponsor” for Investigational Medicinal Product that is used according to a CTA or equivalent.

# CHAPTER 1 PHARMACEUTICAL QUALITY SYSTEM

## Pharmaceutical Quality System

1.1 ATMPs are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the CTA, MA and any other regulations relevant to the production, control and release of medicinal products as applicable. Special provisions apply for the supply of products that do not meet release specifications where there is no alternative treatment available and these are described in 5.49 of this Annex. (Replaces PICS GMP Guide Part I Section 1.4, xv)

## Quality Control

1.2 The finished products and active substances comply with the qualitative parameters and quantitative composition (including purity required and the correct gene sequence) approved in the CTA or MA are correctly labelled and are enclosed within their proper containers;

## Quality Risk Management

1.3 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing through to product discontinuation. Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of ATMP active substances and products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, Quality Risk Management (QRM) principles as detailed in Annex 20 are particularly important for this class of materials and should be used to develop their control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination. (Replaces PICS GMP Guide Part I Section 1.2)

# CHAPTER 2 PERSONNEL

## Personnel Hygiene

2.1 The health status of personnel should be taken into consideration for product safety. Where necessary, personnel engaged in production, maintenance, testing and inspections should be vaccinated with appropriate specific vaccines and have regular health checks.

2.2 Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area and appropriate records kept. Health monitoring of staff should be commensurate with the risk; medical advice should be sought for personnel involved with hazardous organisms.

2.3 Every person entering the manufacturing areas should wear clean protective garments appropriate to the operations to be carried out.
Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning

staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where 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, the contamination control measures should be based on QRM principles. (Replaces PICS GMP Guide Part I Section 2.18)

# CHAPTER 3 PREMISES AND EQUIPMENT

# PREMISES

## Production Areas

3.1 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. QRM principles should be used to assess and control the risks. Depending on the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some ATMPs. Segregated production areas should be used for the manufacturing of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. (Replaces PICS GMP Guide Part I Section 3.6)

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

3.3 Concurrent production of two different ATMPs/batches in the same area is permitted under the following conditions:

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

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

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

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

(e) 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.

(f) 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.

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

3.4 The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality.

3.5 Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses): these activities should take place in a segregated area. Dedicated production area should be used for the manufacture of pathogenic organisms. (i.e. Biosafety level 3 or 4), in accordance with national law.

3.6 Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.

3.7 Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks of these raw materials may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign. (Replaces PICS GMP Guide Part I Section 3.13)

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

3.9 Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.

3.10 Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Local regulation must be complied with to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials. (Replaces PICS GMP Guide Part I Section 3.11)

3.11 The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, yeasts, moulds, anaerobes, etc.) where indicated by the QRM process. (Replaces PICS GMP Guide Part I Section 3.1)

3.12 Where processes are not closed and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process, (e.g. during

additions of supplements, media, buffers, gasses, manipulations) then this must be in a working environment with air particle counts, microbial colony counts and other clean room parameters equivalent to those defined in Annex 1. The appropriate level of air classification should be determined having regard to the specific risks, considering the nature of the product and the manufacturing process. (Replaces PICS GMP Guide Part I Section 3.1)

3.13 A less stringent environment than specified in 3.12 above may be acceptable where approved by the competent authority. This should be considered only when a product is intended to treat a life-threatening condition where circumstances necessitate a less stringent environment and manufacturing alternatives do not exist or are not suitable. In this case, the environment must be specified and justified to provide patient benefit that outweighs the significant risk created by manufacturing under less stringent environments. It must be demonstrated that the chosen environment is suitable for maintaining critical quality and safety attributes, taking into account the intended purpose, the mode of application and the health status of the recipient. (Replaces PICS GMP Guide Part I Section 3.1)

3.14 Performing a manufacturing step in premises that are not under direct control of the MAH or Sponsor, (including for example placing equipment used to perform manufacturing steps in hospital wards or theatre), is permissible provided that the MAH or Sponsor demonstrates that the process maintains its validated status utilising the provisions of Annex 15 and any derogation from the mandated standards in this Annex are justified utilising QRM principles described Annex 20, and subject to approval by the competent authority.

## EQUIPMENT

3.15 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard. In addition to that, if single use systems are used, the manufacturer should take in account and verify the impact on the product from extractable, leachable, insoluble particulate and insoluble matter derived from such systems. (Replaces PICS GMP Guide Part I Section 3.39)

3.16 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.

3.17 Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination during processing.

3.18 Primary containment[2] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

3.19 Bioinformatics systems used to support manufacturing must be qualified in accordance with Annex 11 and 15. Any analytical testing performed on materials not used in

[2] See main GMP Glossary on ‘Containment’.

manufacturing but that support bioinformatics informing the manufacturing process (e.g. patient gene sequencing) must be validated. Such analytical equipment is expected to be qualified prior to use.

# CHAPTER 4 DOCUMENTATION

## Retention of Documents

4.1 Traceability records must be retained 30 years after the expiry date of the product unless otherwise specified in the MA or national law. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements apply to blood components in regards to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products. Human cells including haematopoietic cells must comply with the principles laid down in national law with regards to traceability. (Replaces PICS GMP Guide Part I Section 4.11)

4.2 When xenogeneic cells are used as starting materials for ATMPs, information permitting the identification of the donor animal should be kept for 30 years unless otherwise specified in the MA or national law. (Replaces PICS GMP Guide Part I Section 4.11)

## Specifications & Traceability

4.3 Specifications for ATMP starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

4.4 Some products may require specific definition of what materials constitutes a batch. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

4.5 Where human cell or tissue is used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health-related information.

4.6 For starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells/tissues/virus originates (or, as appropriate, the identification of the cell-line, master cell bank, seed lot) should also be described.

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

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

# CHAPTER 5 PRODUCTION

## General

5.1 ATMPs must comply with the applicable national requirements on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

5.2 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.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed information. Material of biological origin with unknown adventitious agent status should be treated in a way to avoid mix-up and cross-contamination. (Replaces PICS GMP Guide Part I Section 5.3)

5.4 At every stage of processing, materials and products should be protected from microbial and other contamination. Appropriate cross-contamination control measures and monitoring strategies should be implemented. Particular consideration should be given to the risk of cross-contamination between cell preparations from different donors with various health statuses. (Replaces PICS GMP Guide Part I Section 5.10)

5.5 PICS GMP Guide Part I Section 5.11 is not applicable to this class of products

5.6 Labels applied to containers, equipment or premises should be clear, unambiguous and in the manufacturer's agreed format. For products containing cells derived from human cell or tissue, donor's labels should contain all relevant information that is needed to provide full traceability. In the case of products for autologous use, the unique patient identifier and the statement "for autologous use only" should be indicated on the immediate label. Alternative approaches/ measures are permitted as long as the risk of erroneous administration of the product is adequately mitigated. (Replaces PICS GMP Guide Part I Section 5.13)

5.7 If closed systems are used for the production of ATMPs, checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state. Special attention should be given to apply these tests to automated systems. The integrity of single use equipment should be verified prior to every use. The integrity of reused equipment should be verified prior to and after cleaning and sterilisation.

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

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

5.10 The use of technologies (e.g. processing inside sterile disposable kits, or processing using closed, automated, manufacturing platform or incubation in closed flasks, bags or fermenters) in a grade C environment may be acceptable if adequate control measures are implemented to avoid the risk of cross-contamination (e.g. appropriate control of materials, personnel flows and cleanness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher grade.

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

## Prevention of Cross-contamination in Production

5.12 An evidence-based QRM process should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including: vectors used and the risk of occurrence of replication competent virus (including different level of risk derived from the use of replication limited, replication defective, conditional replication and replication incompetent vector), facility/equipment design and use, personnel and material flow, microbiological and other adventitious agent controls, characteristics of the critical starting materials/active substance and raw materials, process characteristics, clean room conditions, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the QRM process should be the basis for determining the process workflow and necessity for and extent to which premises and equipment should be dedicated or single-use equipment should be used for a particular product. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified. (Replaces PICS GMP Guide Part I Section 5.20)

5.13 In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

5.14 Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism or groups of related organisms.

5.15 If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.

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

5.17 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).

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

5.19 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:

(a) Segregated premises.
(b) 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.
(c) Use of “closed systems” for processing and material/product transfer between equipment.
(d) Use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area.
(e) Utilisation of single use disposable technologies.
(f) Adequate cleaning procedures. The cleaning procedure (technique, number of sanitation steps, etc.) should be adapted to the specific characteristics of the product and of the manufacturing process. A risk-assessment should be used to determine the cleaning/decontamination procedures that are necessary, including the frequency thereof. As a minimum, there should be appropriate cleaning/decontamination between each batch. The cleaning/decontamination procedures should be validated
(g) 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. 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. (Replaces PICS GMP Guide Part I Section 5.21)

## Validation

5.20 Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions should be recorded, in particular:

(a) All aseptic and sterilisation processes for investigational and authorized ATMPs are expected to be validated to the extent of routine production.
(b) Viral clearance or the removal of any biological contamination that might be a risk for patient safety should be validated.
(c) The methods used for disinfection, should be validated.
(d) For all aseptic processes, aseptic process simulations should be performed as part of initial validation and normally repeated every six months. See Annex 1 for more information. In the case of infrequent production (i.e. if the interval between the production of two batches is more than six months but less than a year), it is acceptable that the process simulation test is done just before the manufacturing of the next batch, provided that the results of the process simulation test are available prior to the starting of production.

(e) If the ATMP is not produced on a routine basis (i.e. over a year) the aseptic process simulation should be conducted in triplicate prior to the start of manufacturing, involving all relevant operators. (Replaces PICS GMP Guide Part I Section 5.23)

5.21 The limited availability of the cells/tissues which is typical for most ATMPs requires the development of approaches to process validation that take into account the quantities of tissue/cells available and that focus on gaining maximum experience of the process from each batch processed. Additional in-process testing to demonstrate consistency of production should where possible offset reduced process validation. ATMPs manufactured for early phase clinical trials (phase I and phase I/II), are not expected to be validated to the extent necessary for routine production

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

5.23 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.

## Control of Starting Materials and Raw Materials

5.24 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 minimizing as much as possible the variability of the starting and raw materials. Specifications related to the product (such as those in Pharmacopoeia monographs, CTA, or MA), will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked.

5.25 The controls required for the quality of starting materials and on the aseptic manufacturing process, particularly for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, assume greater importance. For autologous cell therapies, the maintenance of the aseptic processing from time of collection through manufacturing and administration back into the patient should be ensured. Where a CTA or MA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

5.26 The ATMP manufacturer should verify compliance of the supplier’s materials with the agreed specifications. The level of oversight and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials. (Replaces PICS GMP Guide Part I Section 5.35).

5.27 In addition to the specifications for the starting materials, the agreement between the ATMP manufacturer (or, as appropriate, the sponsor or MAH) 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. (Replaces PICS GMP Guide Part I Section 5.28)

5.28 The MAH should define critical materials, for the process based on process knowledge and QRM process.

5.29 The selection, qualification, approval and maintenance of suppliers of starting materials, raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) and materials that come in direct contact with the products during manufacture and storage (e.g. single use equipment) together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of oversight should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, these materials should be purchased directly from the manufacturer. (Replaces PICS GMP Guide Part I Section 5.27)

5.30 The quality requirements established by the manufacturer for the starting materials and materials, defined to be critical during QRM process, should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification. (Replaces PICS GMP Guide Part I Section 5.28)

5.31 For the approval and maintenance of suppliers of critical materials, the following is required: (Replaces PICS GMP Guide Part I Section 5.29)

ATMP Active substances

The supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance should be available and be retained by the manufacturer of the medicinal product.

Raw materials

The risk of contamination from the relevant raw materials should be assessed by a QRM process prior to setting up the manufacturing process and whenever a change of the respective raw material is implemented.

Appropriate measures should be put in place to reduce risks to the quality of the raw materials.

Material directly in contact with product during manufacture and storage

All material that comes in direct contact with the medicinal product should be of sufficient quality. The risk for cross-contamination due to microbiological contamination, extractable and leachable should be assessed especially for single use material (e.g. cell cultivation vessels, cryostorage containers).

A regular qualification of the manufacturers and distributors of all materials to confirm that they comply with the relevant GMP requirements should be performed. Whether an on-site audit needs to be performed at a manufacturer's or distributor's premises should be defined based on QRM process. Generally, audits need to be performed at vendors of all critical materials. Refer to provisions detailed in Chapter 7 as modified by this Annex.

5.32 Only critical materials which have been released by the Quality Control department and which are within their retest date should be used. Where the necessary tests take a long time, it may be permissible to process critical materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. (Replaces PICS GMP Guide Part I Section 5.34)

5.33 PICS GMP Guide Part I Section 5.39 is not applicable to these products

## Human Tissues and Cells Used as Critical Starting Materials

5.34 The donation, procurement and testing of human tissues and cells used as critical starting materials for ATMPs should be in accordance with national law.

(a) Their procurement, donation and testing is regulated in some countries. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting material supplier management.

(b) Where such human cells or tissues are imported they must meet equivalent national standards of quality and safety. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national law.

(c) There may be some instances where processing of cells and tissues used as starting materials for ATMPs will be conducted at tissue establishments. This is permissible only when the material would be otherwise compromised and processing involves only minimal manipulation.

(d) Tissue and cells are released by the Responsible Person (RP) in the tissue establishment before shipment to the medicinal product manufacturer, after which normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer provided controls are in place to prevent cross-contamination with tissue and cells that have been released by the RP in the tissue establishment.

(e) The transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The

manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

(f) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues, should be maintained.

(g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MAH) which defines the tasks of each party.

## Seed Lot and Cell Bank System

5.35 If the production of ATMP involves cell culture or propagation in embryos and animals, in order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, it should be based on a system of master and working virus seed lots and/or cell banks.

5.36 The number of generations (doublings, passages) between the seed lot or cell bank, the ATMPs active substance and finished product should be consistent with specifications in the MA or CTA.

5.37 As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under circumstances which are demonstrably appropriate. 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 or by the same persons. For stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, 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.

5.38 Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

5.39 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, based on QRM principles, for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take into account the infectious nature of the materials to prevent cross-contamination.

5.40 Cell based medicinal products are often generated from a cell stock obtained from limited number of passages. In contrast with the two-tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be covered by a validation protocol.

5.41 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, with frequency based on QRM principles, and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

5.42 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.

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

## Packaging Operations

5.44 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Sterility and/or low bioburden requirements should be adhered to. Different products should not be packaged in close proximity unless there is physical segregation. (Replaces PICS GMP Guide Part I Section 5.49)

## Release

5.45 Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorised Person. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant national competent authority. Generally, a finished product that does not meet release specification should not be administered to a patient unless the provisions given below in 5.46 are met;

5.46 Where authorised by national law, the administration of a product that does not meet the release specification, might be performed in exceptional circumstances (such as when there is no alternative treatment available that would provide the same therapeutic outcome and the administration of the failed products could be lifesaving).

The responsibility and the decision of the patient treatment are solely of the treating physician and is beyond the remit of this PIC/S Annex. The Authorised Person, the MAH and or the Sponsor of clinical trial should consider the following in making the product available:

(a) The batch manufacturing records and the documentation provided to the treating physician should clearly state that the batch has failed the release specifications and describe the parameters that have not been met;

(b) The Authorised Person may provide a less technical description of the failed parameters upon request to the treating physician and where possible a description of potential consequences; and

(c) The Authorised Person (or delegate) should report within 48 hours the supply of the product to the relevant competent authorities, on behalf of the MAH in accordance with their legal obligations.

## Batch release process in cases of decentralised /point of care manufacturing

5.47 There may be cases where manufacturing of the ATMP takes place in sites close to the patient (e.g. ATMPs with short shelf-life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, advantages of using automated equipment, etc.). This includes manufacturing models where partial manufacturing occurs at a central site and finishing occurs at a local site. It also includes manufacturing models where there are no steps occurring at a central site and the active substance is provided to a number of local sites where full manufacture occurs. In such cases, steps in the manufacturing of the ATMPs may occur in multiple sites that may be also located in treatment centres (point of care) including hospitals.

5.48 The batch certification and release process become particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and checked in accordance with the requirements of the CTA or MA and other relevant regulatory requirements including compliance with GMP. The steps of the batch certification and release process should be laid down in a standard operating procedure (SOP). The following conditions need to be respected:

(a) A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. The responsible site:

i. must have availability of an Authorised Person,
ii. must ensure that those involved in the batch certification and release process are adequately qualified and trained for their tasks,
iii. should perform audits to confirm compliance with the batch certification and release process (as descripted in SOP),
iv. must ensure that there is a written contract/technical agreement between the responsible site and the decentralised sites establishing the responsibilities of each party, and
v. must ensure that there are written arrangements to:
   - timely report quality defects, deviations or non-conformity to the central site,
   - ensure deviations are investigated to identity root causes and implement corrective and preventive measures as appropriate, and
   - ensure deviations are approved by a responsible person (after having assessed the impact on quality, safety and efficacy), with the involvement of the Authorised Person as appropriate.

(b) The Authorised Person should have ultimate responsibility for the batch certification (responsibility cannot be delegated). However, it should be possible for the Authorised Person of the responsible site to rely on data/information that is transmitted to him by qualified and trained personnel at the decentralised sites. In certain exceptional cases (for example, different time zones or unexpected release that has to occur at night time) and when permissible according to national law, when the release of the product is needed to address life threatening conditions, the Authorised Person may delegate the release to personnel at the decentralised site that act under the direction of the authorised person, under the following conditions:

i. There is a detailed algorithm that determines the cases when the product can be released at the local site without the preliminary approval of the Authorised Person, including deviations that do not require the intervention of the Authorised Person. If technology permits this step can be performed by a validated computer system;

ii. The Authorised Person reviews all releases that have occurred at the sites within an appropriate timeframe (i.e. no longer than a monthly interval) to confirm the adequacy of the releases including:

- determining that the local sites can continue release
- if any product needs to be recalled or going through hazard alert
- if any provision in the release procedure and /or technical agreement needs modification; and
- the product has not been released without Authorised Person authorisation when required.

# CHAPTER 6 QUALITY CONTROL

6.1 In-process controls have a greater importance in ensuring the consistency of the quality of ATMPs than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.

## General

6.2 The person responsible for quality control should assume responsibility for control of raw materials, starting materials, medical devices that are used in combined ATMPs, packaging materials, intermediate, bulk and finished products (including approval or rejection thereof). In case of autologous products or allogeneic products in a donor-matched scenario, the match between the origin of the starting material and the recipient should be verified (information on the origin of the cells/tissues should be checked).

6.3 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach. Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the MA or CTA, a modified testing and sample retention strategy may be developed and documented. (Replaces PICS GMP Guide Part I Section 6.12)

6.4 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions. When containers are too small, the use of bar-codes or other means that permit access to this information should be considered. (Replaces PICS GMP Guide Part I Section 6.13)

6.5 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 CTA or MA. However, it is acknowledged that this may not always be feasible due to scarcity of the materials or limited size of the batches (e.g. autologous products, allogeneic products in a matched donor scenario, products for ultra-rare diseases, and products for use in first-in-man clinical trial with a very small scale production).

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

6.7 A sample of a fully packaged unit (retention sample) should be kept per batch for at least two years 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 what 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.

6.8 The retention period of samples of starting materials, active substance and intermediate product should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be justified. In cases of short shelf-life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf-life (such as cryopreservation) is representative for the intended purpose. For instance, cryopreservation 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).

## Testing

6.9 For cell-based ATMPs, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detection fastidious organisms where appropriate.

6.10 Batch certification of short shelf life products performed prior to completion of all end product quality control is permitted when the short shelf life, due to the testing timelines, would not allow for effective distribution to a patient. In this occurrence there must be a suitable control strategy in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls

and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation.

Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages:

(a) Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the Authorised Person.

(b) Assessment of the final analytical tests and other information available for final certification by the Authorised Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

### On-going stability programme

6.11 The methodology in the on-going stability programme can differ from the approach followed to obtain the stability data submitted in the MA application (e.g. different frequency of testing), provided that it is justified. Stability studies on the reconstituted product are performed during product development and need not be monitored on an on-going basis. The use of surrogate materials, (i.e. material derived from healthy volunteers) or alternative scientifically sounds approaches, are acceptable in case of autologous products (or matched donor scenario) where the batch needs to be administered in its entirety to the patient. (Replaces PICS GMP Guide Part I Section 6.31)

## CHAPTER 7 OUTSOURCED ACTIVITIES

### OTHERS

7.1 Collection of starting materials and highly specialised testing in the jurisdictions that are subject to licensing (e.g. karyotype testing, exome sequencing) can be outsourced to non GMP licensed third party, as allowed by national law, provided that:

(a) There is a rationale and a justification in the quality system

(b) The contract giver takes responsibility to ensure that the contract acceptor demonstrates an appropriate level of GMP commensurate to the risk to the product and the activities performed using the principles of Annex 20

(c) That proportionate qualifications/validations as appropriate are conducted (with reference to Annex 15 and Annex 20) to demonstrate that the activities are not detrimental to the quality of the product manufactured.

# CHAPTER 8 COMPLAINTS AND PRODUCT RECALL

## PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS

8.1 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 preventive measures is also required.

8.2 A product defect alert should be issued, in the cases of single batch products or when there is no alternative product available at the time and/or for which a recall action will result in a significant interruption of patient treatment either of which would likely present greater adverse clinical sequelae than the defect itself. The product defect alert- allows for the informed, continued use of defective but critical ATMPs, raises awareness of the issue and describes the precautionary actions that clinicians or patients may take to mitigate any associated risk.

8.3 In order to test the robustness of the recall procedure, in the case of authorised ATMPs, consideration should be given to the possibility of performing mock-recall actions. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations. However, it is acknowledged that a mock-recall action may not be appropriate in certain settings, e.g. autologous ATMPs, allogeneic ATMPs in a matched donor scenario, ATMPs where the time between manufacturing and administration of the product to the patient is very short. (Replaces PICS GMP Guide Part I Section 8.30)

# PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

## B1. ANIMAL SOURCED PRODUCTS

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[3] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

B 1.1 Monitoring programmes should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.

B 1.2 Where abattoirs are used to source animal tissues; they should be shown to operate to stringent standards. Account should be taken of reports from national regulatory organisations which verify compliance with the requirements of food, safety, and quality veterinary and plant health legislation.

[3] See PIC/S GMP Chapter 5.

B 1.3 Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside PIC/S GMP but should be shown to provide equivalent levels of control.

B 1.4 Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

B 1.5 Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

B 1.6 The use of cells, tissues and organs from wild animals is not permitted.

## B2. GENE THERAPY PRODUCTS

There are potentially 2 types of gene therapy products (vectors and genetically modified cells) and both are within the scope of the guidance in this section. For cell-based gene therapy products, some aspects of guidance in section B3 may be applicable.

B2.1 Starting material:

(a) For genome editing approaches, the starting materials shall be, as appropriate, the vector (viral or non-viral vector) carrying the DNA sequences encoding the modifying enzyme, the mRNA expressing the modifying enzyme, the modifying enzyme itself, the genetic sequence for modification of the cell genome (e.g. a regulatory guide RNA) or a ribonucleoprotein (e.g. Cas9 protein pre-complexed with gRNA), the repair template (e.g. linear DNA fragment or a plasmid), and the components to produce them. When vectors, mRNA or proteins are used, the principles of GMP shall apply from the bank system used to produce these materials onwards.

(b) For medicinal products based on induced pluripotent stem (iPS) cells generated by genetic modification, the principles of GMP and the scientific recommendations given in this guideline should apply after procurement of the cells including the generation of iPS cells and the subsequent selection process. It is acknowledged that at the early steps in iPS cells generation, cell material may be limited and availability of samples may impact the extent of testing and process qualification.

(c) For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids used to transfect the packaging cells and the MCB of the packaging cell line.

(d) For products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells.

(e) For genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations.

The principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.

B2.2 Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials; cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant. ATMPs in which the starting materials are obtained from animals (xenogeneic) should follow provisions laid out in section B1.

B2.3 Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimise risk. This strategy should be used as a basis for the design of the process, the manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

B2.4 The manufacture and testing of gene therapy medicinal products raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. Legislated local and, if applicable, international safety measures should be applied.

B2.5 Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles, where possible utilising unidirectional flows. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.

B2.6 Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated.

B2.7 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.

B2.8 An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

B2.9 Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible, sample collection additions and transfers should prevent the release of viral material.

B2.10 A description of the production of vectors and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non-viral vector stock) to the finished product.

B2.11 Shipment of products containing and/or consisting of GMO should conform to appropriate national law.

B2.12 The following considerations apply to the ex-vivo gene transfer to recipient cells:

(a) Measures (including considerations outlined under paragraph 3.5 in Part A) to minimise the potential for cross-contamination and mix-up between cells from different patients are required. This should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector.

(b) Traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s).

(c) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.

## B3 SOMATIC HUMAN AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS AND COMBINED ATMPs

For genetically modified cell-based products that are not classified as GT products, some aspects of guidance in section B2 may be applicable.

B3.1 Use should be made, where they are available, of authorised sources (i.e. licensed medicinal products or medical devices which have gone through a conformity assessment procedure) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices).

B3.2 Where devices, including custom-made devices, are incorporated as part of the products:

(a) There should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device.

(b) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.

B3.3 Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors or related to cell pooling. The robustness of the control and test measures put in place for these source materials should be ensured. Animals from which tissues and cells are collected should be reared and processed according to the principles defined in the relevant guidelines. Somatic cell therapy medicinal products (SCTMPs), tissue engineered products (TEPs) and combined ATMPs in which the starting materials are obtained from animals (xenogeneic) should follow Section B1.

B3.4 Careful attentions should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.

B3.5 Where relevant, a stability-monitoring programme should be in place together with reference and retain samples in sufficient quantity to permit further examination.

# COMMON GLOSSARY TO ANNEX 2A and 2B

Entries are only included where the terms are used in Annex 2 and require further explanation. Definitions which already exist are cross-referenced only.

**Active substance**

The active substance of a product is defined in the relevant CTA or MA authorisation dossier.

- For cell based ATMPs are generally cells of mammalian or human origin.
- For gene therapy products might be recombinant biological constructs (e.g. nucleic acid vectors, viruses).

**Adjuvant**
A chemical or biological substance that enhances the immune response against an antigen.

**Advance Therapeutic Medicinal Products (ATMP)**
ATMP means any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products. ATMPs may incorporate, as an integral part of the product, one or more medical devices, in which case they are referred to as “Combined ATMPs”

**Allergoids**
Allergens which are chemically modified to reduce IgE reactivity.

**Antigens**
Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.

**Antibody**
Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may be divided into 2 main types based on key differences in their method of manufacture:

**Monoclonal antibodies (MAb)**
Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

**Area**
A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air handling unit.

**Biological Starting Material**
Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (for example, cell substrates, host/vector production cells, eggs, viral strains, etc.).

**Bioburden**
The level and type (i.e. objectionable or not) of micro-organism present in raw materials, media, biological substances, intermediates or products. Regarded as contamination when the level and/or type exceed specifications.

**Biological medicinal product** A biological medicinal product is a product, of which the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the

determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

**Biosafety level (BSL)**
The containment conditions required to safely handle organisms of different hazards ranging from BSL1 (lowest risk, unlikely to cause human disease) to BSL4 (highest risk, cause severe disease, likely to spread and no effective prophylaxis or treatment available).

**Campaign manufacture**
The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment.

**Closed system**
Where an active substance or product is not exposed to the immediate room environment during manufacture.

**Contained use**
An operation, in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which barriers (physical / chemical / biological) are used to limit their contact with the general population and the environment.

**Critical materials**
Are all materials that have a significant negative impact on product quality and patient safety if their quality is impaired. **Starting materials, raw materials and single use equipment** or primary packaging materials and any other material in direct contact with the product during manufacture could fall under the definition of critical materials depending on the nature of the individual medicinal product and the manufacturing process.

**Ex-vivo**
Where procedures are conducted on tissues or cells outside the living body and returned to the living body.

**Feeder cells**
Cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human embryonic fibroblasts that have been treated to prevent them from dividing.

**Fermenter**
In case of (mammalian) cell lines the term fermenter should be understood as bioreactor.

**Gene**
A sequence of DNA that codes for one (or more) protein(s).

**Gene transfer**
A process to transfer a gene in cells, involving an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. After gene transfer, genetically modified cells are also termed *transduced cells*.

**Genetically modified organism (GMO)**
Means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

**Hapten**
A low molecular weight molecule that is not in itself antigenic unless conjugated to a 'carrier' molecule.

**Hybridoma**
An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumour cells.

**In-vivo**
Procedures conducted in living organisms.

**Look-back**
Documented procedure to trace ATMPs active substances or products which may be adversely affected by the use or incorporation of animal or human materials when either such materials fail release tests due to the presence of contaminating agent(s) or when conditions of concern become apparent in the source animal or human.

**Master cell bank (MCB)**
An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks.

**Master virus seed** (MVS) – as above, but in relation to viruses;

**Master transgenic bank** – as above but for transgenic plants or animals.

**Multi-product facility**
A facility that manufactures, either concurrently or in campaign mode, a range of different ATMPs active substances and products and within which equipment train(s) may or may not be dedicated to specific substances or products.

**Plasmid**
A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome; it can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

**Primary cell lot**
A pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications**.**

**Raw materials**
Are all materials that come in direct contact with the product during the manufacturing process but are not necessarily part of the final formulation (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors).

**Responsible Person (RP) for blood or tissue establishment.**
This term is equivalent to the EU term "Responsible Person".

**Scaffold**
A support, delivery vehicle or matrix that may provide structure for or facilitate the migration, binding or transport of cells and/or bioactive molecules.

**Somatic cells**
Cells, other than reproductive (germ line) cells, which make up the body of a human or animal. These cells may be autologous (from the patient), allogeneic (from another human being) or xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo, to be administered in humans to obtain a therapeutic, diagnostic or preventive effect.

**Specified pathogen free (SPF)**
Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from groups (e.g. flocks or herds) of animals free from specified pathogens (SPF). 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.

**Transgenic**
An organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

**Vector**
An agent of transmission, which transmits genetic information from one cell or organism to another, e.g. plasmids, liposomes, viruses.

**Viral vector**
A vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes; if the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

**Viral Vector replication limited / defective / conditional replication**
A constrained ability to replicate where the intent is for the vector may be to target a particular tissue or target cell type with a planned integration required for clinical efficacy of the gene therapy.

**Viral Vector replication incompetent / devoid**
No ability of the vector to replicate.

**Working cell bank (WCB)**
A homogeneous pool of cells, that are distributed uniformly into a number of containers derived from a MCB that are stored in such a way to ensure stability and for use in production.

**Working virus seed (WVS)**
As above but in relation to viruses, **working transgenic bank** – as above but for transgenic plants or animals.

**Zoonosis**
Animal diseases that can be transmitted to humans.