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, ex vivo and in vivo genome-editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or of animal origin (xenogeneic cells), either primary or established cell lines. In a medicinal product, the genetically modified cells or gene therapy products can be presented alone or combined with medical devices.

This annex provides additional and specific guidance on the full range of ATMPs (as defined in the glossary) and the active substances that are used in their manufacture. This annex applies both to investigational ATMPs and market-authorised ATMPs. It can also be applied to ATMP manufacturing in hospital settings and for compassionate use programs, where authorised by national law.

Although one of the objectives of this present annex 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.

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.

APPLICATION OF THIS ANNEX

This annex, along with several other annexes of the Guide to GMP, provides guidance, which supplements that in Part I: *Basic Requirements for Medicinal Products* and in Part II: *Basic Requirements for active pharmaceutical ingredients* of the PIC/S GMP Guide. This annex is not a stand-alone document and should be applied in conjunction with PIC/S GMP guidelines and annexes. It has

however been written in a manner that it could enable development of a standalone guide if integrated with PIC/S GMP Part I, Part II, and related annexes.

Where due to the nature of the product or technical necessities, specific guidance is provided in this annex, compliance with this annex is expected and takes precedence over other sections in the PIC/S GMP Guide unless there are good reasons for not doing so with documented sound scientific rationale applied using QRM principles.

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

(a) Tissues and cells used as starting materials of ATMPs may be subject to other national legislation that cover donation, procurement, testing, processing, preservation, storage and distribution.

(b) For blood or blood components used as starting materials for ATMPs, national legislation may provide the technical requirements for the selection of donors and the collection and testing of blood and blood components.

The manufacturing process for ATMPs is product-specific and different design approaches are possible. The appropriate application of GMP should be described, justified in the Clinical Trial Application (CTA) or Marketing Authorisation (MA), and in accordance with national law. Consideration may be given to defining which manufacturing process steps are required to manufacture starting materials, ATMP active substance, or the finished ATMP. In some cases, the manufacturing process between the ATMP active substance and the final product can be defined as continuous.

The manufacture and control of genetically modified organisms also needs to comply with other local, national or regional requirements. Appropriate containment should be established and maintained in facilities where any genetically modified organism is handled. Advice should be obtained according to national law in order to establish and maintain the appropriate Biological Safety Level. GMP should be adhered alongside these requirements.

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 adherence to the GMP or GMP principles for the manufacturing steps indicated in the corresponding table is dependent on applicable national legislation. The level of GMP requirements increases from early to later steps in the manufacture of ATMP active substances. 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. According to national legislation more or less stringent approaches on the application of GMP on those early stages may apply.

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

Example Products	**Application of this Annex (see note[1])**			
Gene therapy: mRNA	Linear DNA template preparation	In vitro cell free transcription	mRNA purification	Formulation, filling
Gene therapy: in vivo viral vectors	Plasmid manufacturing	Establishment of MCB, WCB[2]	Vector manufacturing and purification	Formulation, filling
Gene therapy: in vivo non-viral vectors (naked DNA, lipoplexes, polyplexes, etc.)	Plasmid manufacturing	Establishment of bacterial bank[2]	Fermentation and purification	Formulation, filling
Gene therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue / cells	Plasmid manufacturing	Ex-vivo genetic modification of cells	Formulation, filling
		Vector manufacturing[3]		
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells	Establishment of MCB, WCB or primary cell lot or cell pool[2]	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, filling
Tissue engineered products	Donation, procurement and testing of starting tissue / cells	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool[2]	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling

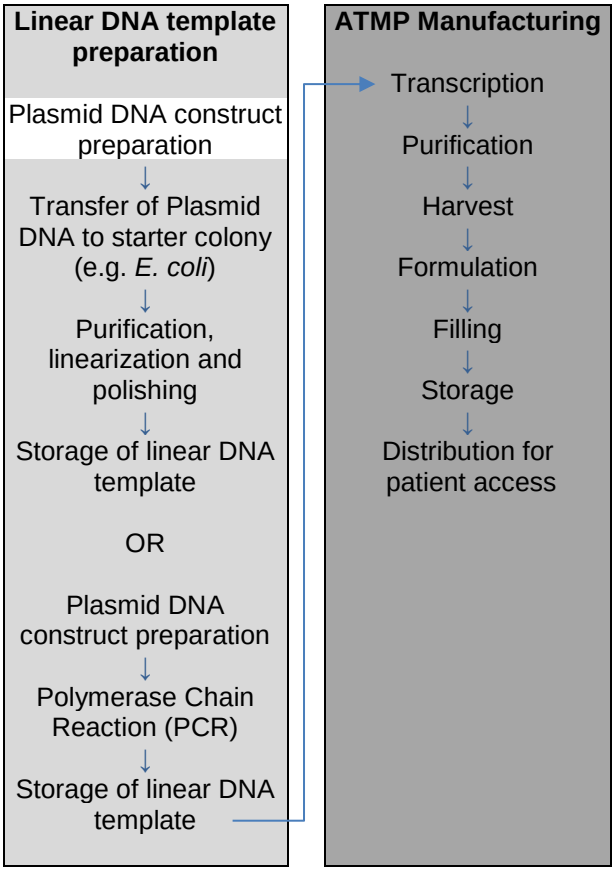
[1] Application of this annex applies to manufacturing steps illustrated in dark grey. Application of this annex or principles of this annex apply to steps illustrated in light grey apply depending on the requirements of national legislation.

[2] Refer to points 5.32 for establishment of cell banks and seed lots.

[3] In the case of gene therapy ex-vivo genetically modified cells, this guide applies to vector manufacturing except where otherwise authorised by national law where principles of GMP should apply.

The following are some non-exhaustive examples in the application of GMP to the manufacture of ATMP.

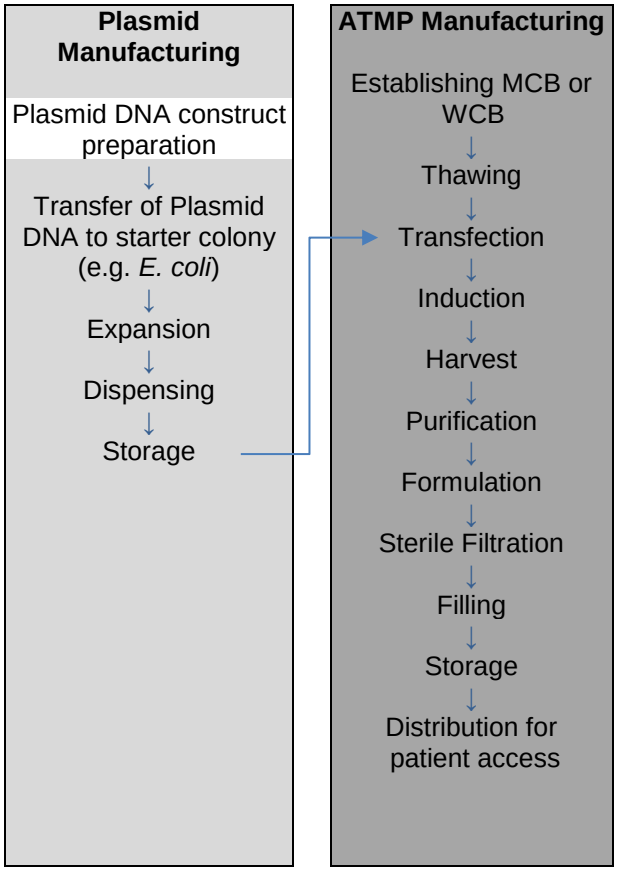
Figure 1: Example of gene therapy mRNA ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- A Marketing Authorisation Holder (MAH) may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

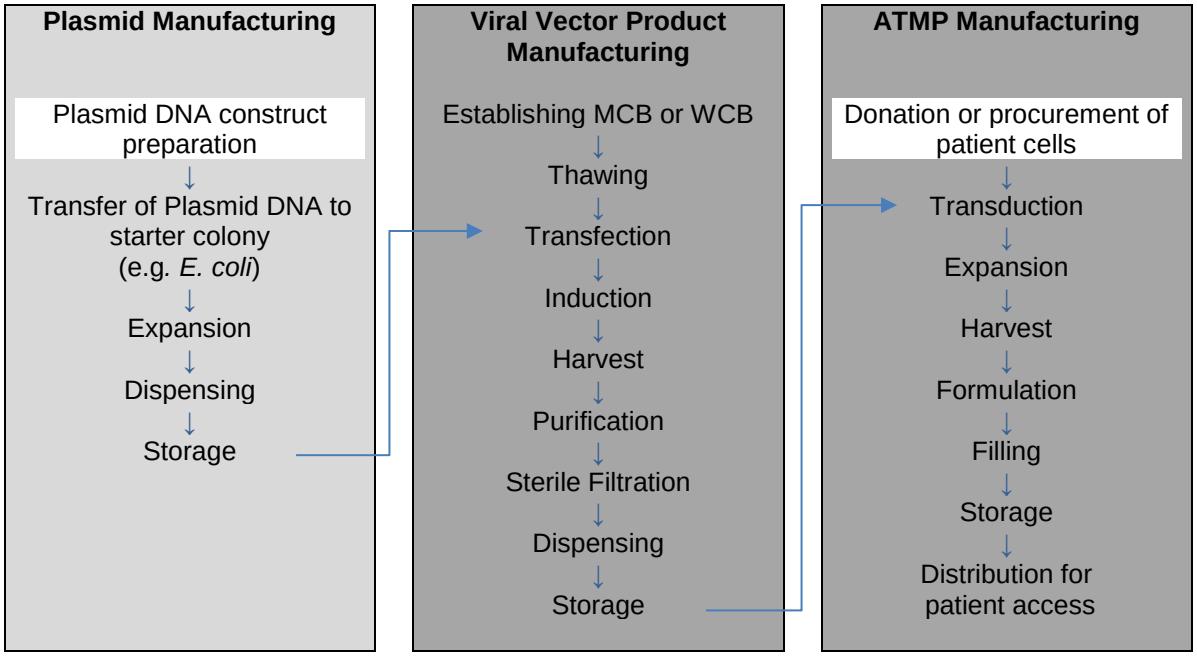
Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- A MAH may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

Figure 3: Example of autologous CAR-T therapy ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with principles of Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- GMP requirements applied to the manufacture of a viral vector should align with Annex 2A and PIC/S GMP Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- The application of this guide does not include the donation or procurement of patient cells.
- A MAH may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

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 an opportunity for extraneous microbial contaminants (e.g. bacteria, fungi) to grow. In addition, some 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 (i.e. engineering and technical controls). In addition, manufacturing processes need to be well designed and controlled so as not to add further variability to the product.

Product specifications such as those in pharmacopoeial monographs, CTA, and MA will dictate whether and to what manufacturing stage 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 and sterile disposable product-contact equipment can significantly reduce the risk of accidental contamination and cross-contamination.

ATMPs require a combination of unique biological methods and standard physico-chemical assays for their Quality Control (QC). For many cell-based products, there is variability introduced through the starting materials that cannot be overcome by the manufacturing process or In-Process Controls (IPCs). Adequate control of the starting and raw materials, well defined characterisation of the ATMP active substance and ATMP drug product release testing form the crucial part of the QC. Controls should take into consideration the intrinsic variability of the biological material needed for ATMP manufacturing. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal 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 ATMP that is used according to a CTA or equivalent.

SUPPLIMENTARY PROVISIONS TO PIC/S GMP GUIDE PART I

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 have a two-step release process (described in Section 6.14) or such that do not meet release specifications where there is no alternative treatment available (described in Sections 6.11 to 6.13). (Replaces PIC/S GMP Guide Part I Section 1.4, xv)

Quality Risk Management

1.2 GMP applies to the lifecycle stages from the manufacture of investigational ATMP, technology transfer, and commercial manufacturing through to product discontinuation. The 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 medicinal products and should be used to develop their control strategy across all stages of development and manufacturing steps to minimise variability and to reduce the opportunity for contamination and cross-contamination. (Replaces PIC/S GMP Guide Part I Section 1.2)

CHAPTER 2 PERSONNEL

2.1 The health status of personnel should be taken into consideration for product safety. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where ATMP active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to the duties assigned to them, including any specific safety measures to protect product, personnel and the environment.

2.2 Any changes in the health status of personnel, which could adversely affect the quality of the product, should prevent work in the production area. Health monitoring of staff should be commensurate with the risk; medical advice should be sought for personnel involved with hazardous organisms. General consideration should be given to Occupational Health & Safety (OH&S) for personnel involved with hazardous substances as required by national law.

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 QC, maintenance and cleaning personnel) should be controlled based on QRM principles.

In general, personnel should not pass from areas of 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 route is unavoidable, a Contamination Control Strategy (CCS) based on QRM principles should be applied (refer to Section 3.4 CCS). (Replaces PIC/S 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 to product quality. QRM principles should be used to assess and control the risks.

Depending on the level of risk presented by some ATMPs and the materials involved in their production (for example, viruses), it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk. Segregated production areas should be used for the manufacture of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. (Replaces PIC/S GMP Guide Part I Section 3.6)

3.2 Concurrent production of two or more different ATMPs/batches in the same area might be permitted due to adequate operational and/or technical control where justified under QRM principles applied across the entire sequence of manufacturing steps. For example:

(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.

(b) When more than one isolator is 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 (BSC) in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities. The simultaneous use of more than one BSC 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 any mix-ups. The rationale should be justified based on QRM principles.

(d) The use of multiple closed systems in the same area is permitted, in the case that their close state can be demonstrated. (refer to point 3.13.)

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

3.4 Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses, replication competent vectors) that should be segregated based on a documented CCS and QRM principles. The manufacturer should justify the level of segregation required based on the CCS and through QRM principles. The outcome of the QRM process should determine the necessity for and extent to which the premises and equipment should be dedicated to a particular product. In some cases, dedicated facilities, dedicated areas or dedicated equipment may be required in accordance with the national law. Simultaneous incubation and/or storage of replication competent vectors/products, or infected materials/products, with other materials/products is not acceptable.

3.5 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.

3.6 If materials (such as culture media and buffers) have to be measured or weighed during the production process, small stocks may be kept in the production area for a specified duration based on defined criteria (e.g. duration of manufacture of the batch or of the campaign). (Replaces PIC/S GMP Guide Part I Section 3.13)

3.7 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 BSCs 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 as defined by Annex 1. The design of such areas should be such that measures put in place to prevent release of material into the surrounding environment should not compromise sterility assurance level (SAL) of the product and vice versa.

3.8 Air vent filters that are directly linked to the sterility of the product (e.g. to maintain the integrity of a closed system) should be hydrophobic, monitored during use (e.g. pressure differential monitoring if appropriate) and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles. If pressure monitoring or integrity testing is technically not feasible for the filter system, vendor supplied information may be considered for approval. However, this has to be taken into account in the CCS as an additional risk factor especially for short shelf life ATMPs, where microbiological quality tests are not available at the time of batch release prior to medical product administration.

3.9 Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. They must comply with national law to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials. (Replaces PIC/S GMP Guide Part I Section 3.11)

3.10 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 microbiological 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 principles.

3.11 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) appropriate environmental conditions should be applied. For aseptic manipulations parameters in line with Annex 1 (i.e. Grade A with Grade B background) should be applied. The environmental monitoring program should include testing and monitoring of non-viable contamination, viable contamination and air pressure differentials. The monitoring locations should be determined having regards to the QRM principles. The number of samples, volume, and frequency of monitoring, alert and action limits should be appropriate taking into account the QRM principles. Sampling methods should not pose a risk of contamination to the manufacturing operations. Where appropriate control is required in the process, temperature and relative humidity should be monitored. All environmental monitoring results should be trended.

3.12 Only in exceptional circumstances when an appropriate manufacturing environment is not available, a less stringent environment than that specified in Section 3.11 above may be acceptable for processes that are not closed where approved by the Competent Authority and in accordance with CTA or MA or other national requirements. However, this option should be considered exceptional and applicable only if the product is intended to treat a life-threatening condition where no alternative therapeutic options exist. The environment must be specified and justified to provide patient benefit that outweighs the significant risk created by manufacturing under less stringent environments. If the Competent Authority grants an approval, the manufacturer must pursue establishing the appropriate environment as improvements in the technology occur.

3.13 For closed systems, a lower classified area than Grade A in background Grade B might be acceptable based on the outcome of a QRM assessment. The appropriate level of air classification and monitoring should be determined having regard to the specific risks, considering the nature of the product, the manufacturing process and the equipment used. QRM should be used to determine whether the technology used supports reduced monitoring, in particular where monitoring can be a source of contamination. This is in addition to:

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

(b) If the closed system can be shown to remain integral throughout the entire usage, a background of Grade D might be acceptable.

Requirements of Annex 1 regarding the provision of closed system should be considered.

3.14 In exceptional circumstances, it is permissible to perform a manufacturing step in premises that are not under direct control of the ATMP manufacturer or MAH (including for example placing equipment used to perform manufacturing steps in hospital wards or theatre) where approved by the Competent Authority and in accordance with CTA or MA or other national requirements. In such cases, it should be demonstrated that the process maintains its validated status in accordance to principles and guidelines in Annex 15, Annex 20 and in this annex. These arrangements should be subject to approval by the Competent Authority. The responsibilities of each parties should be defined in written technical agreements.

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, if single use systems (i.e. disposable systems) are used, the manufacturer should take into account and verify the impact on the product from extractable, leachable, insoluble particulate and insoluble matter derived from such systems. Annex 1 regarding provisions for single use systems should be considered. (Replaces PIC/S 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). Where the relocation of equipment is unavoidable, after reviewing engineering and/ or technical modifications, the risk should be assessed in line with QRM principles, mitigated and monitored to ensure an effective cross-contamination control strategy (refer to Section 3.4 CCS). The qualification status of the equipment moved should also be considered.

3.17 The design of equipment used during handling of live organisms and cells, including those for sampling, should be considered to prevent any contamination during processing.

3.18 Primary containment[4] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

[4] See Main GMP Glossary on ‘Containment’.

3.19 Electronic systems used to support manufacturing must be qualified in accordance with Annex 11 and 15. Any analytical testing performed on materials not used in manufacturing but that support bioinformatics informing the manufacturing process (e.g. patient gene sequencing) should be validated. Such analytical equipment is expected to be qualified prior to use.

CHAPTER 4 DOCUMENTATION

Specifications

4.1 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 and oversight including their microbiological quality.

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

Traceability

4.3 Where human cells or tissues are 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, according to national legislation.

4.4 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.

4.5 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. This system can be manual or automated. It should be used throughout the manufacturing lifecycle to include clinical trial and commercial batches.

4.6 Traceability records should be kept as an auditable document and unequivocally linked to the relevant batch record. The storage system should ensure that traceability data allow for easy access, in case of an adverse reaction from the patient.

4.7 Traceability records for cellular and tissue-based products and for any personalized ATMP must be retained 30 years after the expiry date of the product unless otherwise specified in the MA/CTA 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 applied to blood components in regard 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 concerning traceability.

4.8 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/CTA or national legislation.

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.

Viral safety for gene therapy ATMPs should be ensured by having systems in place that ensure the quality of starting (including cell banks and viral seed stocks) and raw materials through the production process.

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 At every stage of processing, materials and products should be protected from microbial and any other contamination. Appropriate contamination control and monitoring strategies should be implemented (refer to Section 3.4 CCS). Particular consideration should be given to the risk of cross-contamination between cell preparations from different donors and, where applicable, from donors having different positive serological markers. (Replaces PIC/S GMP Guide Part I Section 5.10)

5.4 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 antimicrobials do not interfere with any product microbial contamination testing or sterility testing, and that they are not present in the finished product (unless specifically justified in the CTA or MA).

5.5 Labels applied to containers, equipment or premises should be clear, well defined and in the manufacturer's agreed format.

Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific or autologous product. For products containing cells derived from human cells or tissue, donor's labels should contain all relevant information that is needed to provide full traceability. In the case of autologous products, the unique patient identifier and the statement "for autologous use only" should be indicated on the outer packaging or, where

there is no outer packaging, on the immediate packaging or as otherwise specified in national law.

Alternative approaches/measures are permitted as long as the risk of erroneous administration of the product is adequately mitigated. For investigational ATMPs that are blinded, the requirement to state “autologous use” can be substituted by a barcode or an alternative equivalent mechanism that ensures blinding while maintaining patient safety. (Replaces PIC/S GMP Guide Part I Section 5.13)

5.6 When setting up a programme for primary and secondary 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 and segregation strategies should be applied. (Replaces PIC/S GMP Guide Part I Section 5.49)

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. If feasible and based on QRM principles, for example considering testing carried out by vendors, the integrity of single use systems should be verified at adequate frequency prior to use and potentially post use, possibly automatically. The integrity of reused equipment should be verified before use after cleaning and sterilisation.

5.8 A system is no longer considered closed when materials are added or withdrawn without aseptic techniques (e.g. without use of sterile connectors or filters aseptically connected).

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 due to risk of carryover contamination. 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 Careful attention 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.

5.11 The suitability of selected packaging material should be considered. The adhesiveness, durability and legibility of printed text of labels used for containers that are stored at ultra-low temperatures (- 60 °C or lower) should be verified. Additionally, apply a holistic approach to minimize the risk to container closure integrity (CCI) that can occur during storage at ultra-low temperatures. Evidence-based data should be generated to support the selection of the appropriate primary packaging components and qualification of the container/closure sealing process.

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 to take into account include:

(a) 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 vectors),

(b) facility/equipment design and use,

(c) personnel and material flow,

(d) microbiological and other adventitious agent controls,

(e) characteristics of the starting materials/active substance and raw materials,

(f) process characteristics,

(g) clean room conditions,

(h) cleaning processes, and

(i) analytical capabilities relative to the relevant limits established from the evaluation of the products.

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 systems 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. Results should be reviewed jointly with the CCS.

(Replaces PIC/S GMP Guide Part I Section 5.20)

5.13 The methods used for sterilisation, disinfection, virus removal or inactivation should be validated. In cases where a virus inactivation or removal process is performed during manufacture, measures to avoid the risk of recontamination should be taken. (refer to Section 5.19(a))

5.14 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. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Decontamination measures should be available for each organism or groups of related organisms in line with the QRM process. Decontamination measures should be validated for effectiveness.

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. An assessment of the impact on the immediate products and any others in the affected area should also be made.

5.16 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). For ATMPs that cannot be sterilised, any open processing (e.g. filling) must be conducted aseptically to minimise the introduction of contaminants.

5.17 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.

5.18 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 entire manufacturing facility or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness,

(c) adequate cleaning procedures:

i. the cleaning procedure (technique, number of sanitation steps, etc.) should be adapted to the specific characteristics of the product and of the manufacturing process;

ii. a risk-assessment should be used to determine the cleaning and decontamination procedures that are necessary, including the frequency thereof;

iii. as a minimum, there should be appropriate cleaning and decontamination between each batch; and

iv. all cleaning and decontamination procedures should be validated.

(d) use of “closed systems” for processing and for material or product transfer between individual processing equipment,

(e) use of air locks and pressure cascade to confine potential airborne contaminant within a specified area,

(f) utilisation of single use systems,

(g) other suitable organisational measures, such as the:

i. dedication of certain parts of equipment (e.g. filters) to a given type of product with a specific risk profile;

ii. keeping specific protective clothing inside areas where products with high-risk of contamination are processed;

iii. implementing adequate measures to handling waste, contaminated rinsing water and soiled gowning; and

iv. imposing restrictions on the movement of personnel.

(Replaces PIC/S GMP Guide Part I Section 5.21)

Validation

5.19 During process validation potential limited availability of quantities of tissue/cells has to be taken into account. A strategy on gaining maximum process knowledge has to be implemented.

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

(a) ATMPs manufactured for exploratory, early phase clinical trials (phase I and phase I/II), are expected to be validated proportionately with the knowledge and the risk associated with the respective phase. All aseptic and sterilisation processes as well as virus inactivation or removal for investigational and authorised ATMPs are expected to be validated. The effectiveness of disinfection methods should be proven. For all phases, the principles as outlined in Annex 13 should be applied.

(b) For all aseptic processes, aseptic process simulations should be performed as part of initial validation and repeated thereafter every six months in line with Annex 1. 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 prior to manufacturing of the next batch. This is provided that, the results of the process simulation test are available prior to the starting of production. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.

(c) If the ATMP is not produced on a routine basis (i.e. over a year), the aseptic process simulation should be conducted at least in triplicate prior to the start of manufacturing, involving all relevant operators. QRM principles should be applied in accordance with Annex 1. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.

(d) The use of surrogate material during process validation 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).

(e) 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.

(Replaces PIC/S GMP Guide Part I Section 5.23)

Control of different types of materials including ATMP Active Substances

5.20 For the approval and maintenance of suppliers of materials, the following is required:

ATMP Active substances

The supply chain traceability should be established. 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 ATMP.

Raw materials and process aids

Prior to setting up the manufacturing process and whenever a change of the respective material is implemented, a QRM process should assess the risk of contamination from the relevant materials as well as their influence on the entire manufacturing process and the resulting product. Appropriate measures should be put in place to reduce risks to the quality of the materials.

Material directly in contact with the ATMP during manufacture and storage

All materials that come in direct contact with the ATMP should be of appropriate quality. The risk of microbiological contamination should be assessed especially for single use systems.

(Replaces PIC/S GMP Guide Part I Section 5.29)

5.21 Only materials that have been released by the Quality Unit and that are within their expiration or retest date should be used. Where the results of necessary tests are not available, it may be permissible to process 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 described and assessed under the principles of QRM. In such cases, release of a finished product is

conditional on satisfactory results of these tests. (Replaces PIC/S GMP Guide Part I Section 5.34)

5.22 A regular qualification of the vendors (e.g. 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 principles. Generally, audits need to be performed at vendors of all materials defined as critical for the manufacturing process according to its product risk profile (PRP). Refer to provisions detailed in Chapter 7 as modified by this annex.

5.23 Application of QRM principles to the total supply chain is a critical part of the process to understand the risks to material quality. The principles of quality by design (QbD) as described in ICH Q8 Guideline on Pharmaceutical Development could be applied:

(a) The MAH should define what constitutes ATMP active substances, starting materials, raw materials and other materials such as single use systems, primary packaging materials and any other materials in direct contact with the product during manufacture by means of Product Risk Profiles (PRP). The PRP should be used to justify the levels of control that apply to individual materials.

(b) Establish the Quality Target Product Profile (QTPP) and define the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP) for the ATMP to establish PRP appropriately.

(c) For each material used, identify the risks presented to the quality, safety and function from its source through to its incorporation in the finished product dosage form. Areas for consideration should include, but are not limited to:

i. transmissible spongiform encephalopathy;

ii. potential for viral contamination;

iii. potential for microbiological or endotoxin/pyrogen contamination;

iv. potential, in general, for any impurity originating from the raw materials, or generated as part of the process and carried over;

v. sterility assurance for materials claimed to be sterile;

vi. potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;

vii. environmental control and storage/transportation conditions including cold chain management; if appropriate and

viii. stability.

(d) With respect to the use and function of each material, consider the following:

i. pharmaceutical form and use of the medicinal product containing the material;

ii. function of the material in the formulation, and for gene therapy products the impact on the gene expression of that material;

iii. degree of which the function of the final product is dependent from the material assessed and how likely it is to be controlled further into the manufacturing process (i.e. if the gene sequence is wrong how easily can this be detected and corrected or if the product is contaminated how likely can this be detected or corrected later in the manufacturing process);

iv. time of preparation of the material in respect to the time of administration of the final product;

v. quantity of material with particular reference to the implication of small final product batch sizes (e.g. 5-50 mg);

vi. any known quality defects/fraudulent adulterations, both globally and at a local company level related to the material;

vii. known or potential impact on the CQA and CPP of the ATMP; and

viii. other factors as identified or known to be relevant to assuring patient safety.

(e) Document the risk profile as low, medium, or high based on the above assessment and use this outcome to determine the PRP. On this basis, the MAH should establish and document the elements of PIC/S GMP that are needed to be in place in order to control and maintain the QTPP.

(f) Once the PRP and the appropriate GMP have been defined, ongoing risk review should be performed through mechanisms such as:

i. number of defects connected to batches of respective material received;

ii. type/severity of such defects;

iii. monitoring and trend analysis of material quality;

iv. observation of trends in drug product quality attributes; this will depend on the nature and role of material; and

v. observed organisational, procedural or technical/process changes at the material manufacturer.

(g) Incorporate the PRP into the CTA or MA as applicable.

(h) The QTPP, once approved in the production process by the Competent Authority, should guide the manufacturer through what controls are important and expected and which can be exempted. The manufacturer should have a

control strategy established that justifies the level of testing performed for incoming starting materials.

5.24 Particular attention should be paid to avoiding contamination and to minimising the variability of the materials. Specifications related to the product (such as those in pharmacopoeial 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.

5.25 For products where final sterilisation is not possible and the ability to remove microbial by-products is limited, the controls required for the quality of materials and on the aseptic manufacturing process assume greater importance. Where a CTA or MA provides for an allowable type and level of bioburden, for example at the ATMP active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

5.26 The selection, qualification, approval and maintenance of suppliers of starting materials, raw materials and materials that come in direct contact with the products during manufacture and storage (e.g. single use systems) 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 ATMP. The supporting evidence for each supplier / material approval should be maintained. Personnel 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 or a manufacturer approved supplier. (Replaces PIC/S GMP Guide Part I Section 5.27)

5.27 For starting material of human origin, the agreement between the ATMP manufacturer (or, as appropriate, the MAH) and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information. In particular, this should include test results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply that may have an impact on the quality or safety of the ATMPs manufactured. National laws that are required as part of the donation and procurement of human blood and blood components, haematopoietic progenitor cells, human tissues and cells for manufacturing purposes need to be adhered to. (Replaces PIC/S GMP Guide Part I Section 5.28)

5.28 The quality requirements established by the manufacturer in the MA or CTA for materials classified as critical during QRM process (according to PRP profile) should be discussed and agreed with the suppliers during the product life cycle. 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. (Replaces PIC/S GMP Guide Part I Section 5.28)

Human Blood, Tissues and Cells Used as Starting Materials

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

(a) The procurement, donation and testing of blood, cells and tissues is regulated in some countries. Such supply sites must hold appropriate approvals from the Competent Authority(ies) which should be verified as part of supplier management.

(b) For cell therapies, the maintenance of the aseptic processing from time of procurement of cells through manufacturing and administration back into the patient should be ensured.

(c) 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.

(d) There may be some instances where processing of blood, tissues and cells used as starting materials for ATMPs will be conducted at blood or tissue establishments. This is permissible only if authorised by national law (e.g. the material would be otherwise compromised and processing involves only minimal manipulation).

(e) Blood, tissue and cells are released by the Responsible Person (RP) in the blood or tissue establishment before shipment to the ATMP manufacturer. After that, 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.

(f) A technical agreement clearly defining the responsibilities should be in place between all involved parties (e.g. manufacturers, tissue establishment, sponsors, MAH).

(g) The transport of blood, 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.

(h) 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.

Seed Lot and Cell Bank System

5.30 A system of master and working virus seed lots and/or cell banks is recommended if the production of allogeneic ATMP involves cell culture or propagation in embryos and animals. This can prevent the unwanted drift of properties, which might ensue from repeated subcultures or multiple generations.

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

5.32 As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, as well as maintenance and storage, should be performed under appropriate GMP conditions. 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 all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented.

5.33 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 characterisation 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.

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

5.35 Cell based ATMPs are often generated from a cell stock obtained from limited number of passages. In contrast with the two-tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be addressed in the MA/CTA and thereby covered by a validation and comparability protocol, as the inter-donor variability may change the product.

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

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

5.38 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.

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 head of quality control is responsible for control of ATMP active substances, starting materials, raw materials and other materials such as primary packaging materials and any other material in direct contact with the product during manufacture as well as medical devices that are used in combined ATMPs. Further, the head of quality control is responsible to control the quality of the ATMP throughout all stages of manufacture. 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.

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 worst-case 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 CTA or MA, a modified testing and sample retention strategy may be developed and documented. (Replaces PIC/S 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 a qualified bar code or other means that permit access to this information should be considered. (Replaces PIC/S GMP Guide Part I Section 6.13)

6.5 In line with requirements of Annex 19, a reference sample of a batch of starting material, raw materials, packaging material and finished product should be drawn. 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. In case of a continuous process, where the ATMP active substance will immediately be turned into the ATMP drug product, only a reference sample of the ATMP drug product needs to be drawn. However, it is acknowledged that drawing reference samples 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 trials with a very small-scale production). In these cases, alternative approaches should be justified and authorised in the corresponding CTA/MA.

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 (i.e. matched donor scenario). In other cases, where the scarcity of the materials is also a concern, the sampling strategy may be adapted based on risk assessment and appropriately implemented mitigation measures. For cases where the starting material is an established cell bank system, there is no need to keep cell bank vials specifically for the purpose of reference samples.

6.7 In line with requirements of Annex 19, a sample of a fully packaged unit (retention sample) should be kept per batch for at least one year after the expiry date (national requirements might differ). A retention sample is, however, not expected in the case of autologous products or allogeneic products, where justified (e.g. 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 Shorter retention periods as mentioned in Section 6.6 and 6.7 might be justified based on the stability and shelf life of the product. 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 cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches that are scientifically justified.

On-going stability programme

6.9 The protocol for the on-going stability programme can be different from that of the initial long term stability study as submitted in the MA dossier provided that this is justified and documented in the protocol (e.g. the frequency of testing, or when updating to ICH/VICH recommendations). Stability studies on the reconstituted and thawed 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 entire batch needs to be administered to the patient. (Replaces PIC/S GMP Guide Part I Section 6.31)

Release

6.10 In general, batches of ATMPs should only be released for sale or supply to the market after certification by an Authorised Person. The batch release specifications are not limited to analytical results (also refer to out of specification (OOS) results). In line with PIC/S GMP Guide Part I Sections 1.4 (xv), 2.6. and 6.34 the Authorised Person should assess the quality of each batch considering processing records, results from environmental monitoring, monitoring of process parameters, analytical results and all deviations from standard procedures and protocols. 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 Competent Authority (if applicable) and is controlled appropriately within the manufacturer's quality system. Generally, a finished product that does not meet release specifications should not be administered to a patient unless otherwise justified.

6.11 Where authorised by national law, the administration of a product that does not meet the release specification might be performed under 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).

6.12 In cases, referred to in point 6.11, where product does not meet release specification, the responsibility and the decision of the patient treatment are solely of the treating physician and are beyond the remit of this PIC/S annex. The Authorised Person, the MAH and/or the Sponsor of the clinical trial should consider the following in making the product available:

The treating physician should provide in writing a rationale and/or request to the Authorised Person and MAH.

(a) Batch manufacturing records and 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) When responding to a treating physician's request, the MAH should provide its evaluation of the risks of product administration. However, it is solely the physician's decision to administer the finished product that does not meet release specifications.

(c) The Authorised Person (or delegate) should report the supply of the product to the relevant Competent Authorities, on behalf of the MAH in accordance with their legal obligations.

6.13 The clinical trial Sponsor or MAH should have procedures in place that describe steps to be taken if product does not meet release specification but may be released to permit treatment. Individual instances that do not meet release specifications may be addressed through lot-by-lot release programmes and specific case-by-case, risk-based assessments, where such programs exist within national law.

6.14 For ATMPs with a short shelf life, where established analytical tests might not permit batch certification prior to product administration, alternative methods of obtaining equivalent data should be considered (e.g. rapid microbiological methods).

Subject to approval from the Competent Authority, batch certification of short shelf life products performed prior to completion of all product quality control is permitted when the testing timelines would not allow for effective distribution to a patient.

(a) A suitable control strategy must be in place, built on enhanced understanding of the product and process performance. This must take into account the controls and attributes of starting materials, raw materials and intermediates.

(b) The procedure for batch certification should provide an exact and detailed description of the entire release procedure, including responsibilities of the different personnel involved in assessment of production and analytical data.

(c) The procedure for batch certification and release of short shelf life ATMP may be carried out in two or more stages:

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

ii. 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.

(d) Increased reliance on process validation should be considered as supporting data for batch release in absence of a complete analytical results panel, even in case of investigational ATMP.

(e) A continuous assessment of the effectiveness of the pharmaceutical quality system must be in place. This includes the records being kept in a manner, which permits trend evaluation.

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

6.15 In the exceptional circumstances where approved by the Competent Authority and in accordance with CTA or MA or other national requirements, manufacturing of the ATMP may take place in sites close to the patient (e.g. ATMPs with short shelf life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, 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. National law might require GMP-manufacturing authorisations and/ or authorisations for the procurement and/or manufacture of blood, cells and tissues intended to be used for ATMP manufacturing at the central site and the satellite sites.

6.16 The batch certification and release process becomes particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and quality controlled 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 clearly documented 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. During the product life cycle, 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 identify root cause(s) and implement corrective and preventive measures as appropriate; and

- ensure deviations are approved by a delegated 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 the Authorised Person by qualified and trained personnel at the decentralised sites.

When permitted by national law, the Authorised Person may delegate release to trained and qualified personnel at the decentralised site to act under the direction of the Authorised Person for exceptional situations (e.g. life threatening cases or off-hours). The following conditions apply:

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 a decentralised site within an appropriately justified timeframe to confirm the adequacy of the releases including:

- determining that the local sites can continue release;
- if any product needs to be recalled or a product alert needs to be issued (see recall section in Chapter 8);
- 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 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:

(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; and

(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, a 'look-back' procedure needs to be initiated. This involves an analysis of the risk(s) and of the need for corrective or preventive measures.

8.2 In addition to recalls, other risk-reducing actions may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals which may be important for:

(a) a single batch product (e.g. autologous ATMP where the entire batch has been administered), or

(b) products where patient treatment interruption presents a higher risk than continued use of the recalled product.

In such cases, the MAH/manufacturer needs to provide information to the treating physician and to the Competent Authority. Quality defect notifications, pharmacovigilance signals and other notifications should also be sent as set in national law.

(Replaces PICS GMP Guide Part I Section 8.31)

8.3 In order to test the robustness of the recall procedure (or healthcare professional notification) consideration should be given to performing mock recall or mock transmission of appropriate information to healthcare professionals. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations.

The frequency of the mock recall (or mock transmission of appropriate information to healthcare professionals) should be justified by the manufacturer considering factors such as the stage of the product development and the complexity of the supply. For authorised products, a yearly frequency is recommended unless otherwise justified.

(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[5] 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 is 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 Control measures for starting and 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. Xenogeneic starting material should comply with other national laws.

B 1.3 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 1.4 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 1.5 Cells, tissues and organs intended for the manufacture of xenogeneic cell based medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and documented.

[5] See PIC/S GMP Chapter 5

B2. GENE THERAPY MEDICINAL PRODUCTS (GTMPs)

There are several types of gene therapy products. Synthetic GTMPs are within the scope of the guidance in this section. For cell-based gene therapy products, some aspects of the guidance in Section B3 may also be applicable.

B2.1 The manufacture and testing of GTMPs 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. National requirements and, if applicable, international safety measures should be applied.

B2.2 A description of the production of viral and non-viral vectors, nucleic acids (e.g. plasmids, linear DNA, mRNA, siRNA) 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.

B2.3 The following considerations apply to the ex-vivo gene transfer to recipient cells:

(a) Traceability requirements must be maintained. (refer to Section 4.3 to 4.8)

(b) There should be a clear batch definition, from cell source to final product container(s). (refer Section 4.2)

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

(d) Although the vector used for the manipulation of the cell will not be part of the final product, all early processes (e.g. design to construction to manufacturing of the plasmid, as well as establishment of cell banks) in the manufacture of viral vectors are considered critical and their quality needs to be under control. In the case that due to national requirements the manufacture of viral vectors are not required under full GMP sufficient quality standards (“principles of GMP”) should be applied in their manufacture.

Manufacture of Viral Vectors and Plasmids under “principles of GMP”

B2.4 Annex 2A and elements of Part II of the PIC/S GMP Guide can be considered for the manufacturing of viral vectors and plasmids where appropriate (refer to the examples in light grey in Table 1).

Manufacturers of viral vectors and plasmids should have a quality management system in place that allows them to apply sections of the guideline most relevant to ensure the quality of the starting materials having regard to the relevant risks for the quality, safety and efficacy of the finished product.

B2.5 The ATMP manufacturer is responsible for appropriate quality of the viral vectors and plasmids used as starting materials. Special attention should be given to requirements described in section 5.23 to 5.28 of this guideline.

(a) The ATMP manufacturer should follow national requirements and apply QRM considering the risk presented by the vector to the safety and quality of the ATMP to justify which sections of Annex 2A and elements of Part II of the PIC/S GMP Guide are applicable for manufacture and testing of viral vectors and plasmids. A defined and controlled manufacturing process should be implemented as a result.

(b) Sufficient quality standards should be applied for the manufacture of plasmids used for the establishment of vectors or early stages of mRNA GTMPs (refer to Table 1). The design through to construction of the nucleic acid (plasmid) preparation by molecular biological and in silico methods is considered under the scope of research and development and therefore not part of the respective Annex.

(c) Relevant provisions in Annex 1 are also applicable. The manufacturer should justify the applicability extent using QRM. In general, products that can be sterile filtered should follow the relevant sections in the Annex 1, otherwise aseptic manufacturing provisions should be followed.

B2.6 If the manufacturing of the vectors is outsourced, the ATMP manufacturer should assess the risk presented by the vector to the quality and safety of the ATMP and thereby select a suitable vector supplier that is able to comply with the GMP standards required by national legislation.

The appropriate sections of Annex 2A and elements of Part II of the PIC/S GMP Guide relevant for the specific product should be determined in the agreement between the ATMP manufacturer and the vector manufacturer and cover relevant aspects (e.g. quality management, documentation, raw materials, cell banks, production, testing and control, storage, and other aspects of handling and distribution, as appropriate). In addition the vector manufacturer should be part of the ATMP manufacturer's vendor qualification programme. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials.

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 GTMPs, some aspects of guidance in Section B2 may be applicable.

B3.1 In the manufacture of such products involving human or xenogeneic cells special attention should be given to traceability requirements (refer to Section 4.3 to 4.8) and definition of a batch (refer to Section 4.2).

B3.2 Authorised sources of cellular products, bio-molecules, bio-materials, scaffolds, matrices, and other substances that are licensed medicinal products or medical devices should be used where available.

B3.3 During the life cycle of the product where devices, including custom-made devices, are incorporated as part of the product, an appropriate Quality Agreement should be made between manufacturer and device suppliers to assure consistent quality of the device.

COMMON GLOSSARY TO ANNEX 2A AND 2B

The Glossary in the main GMP Guide applies also to Annex 2A & B. Entries in this common glossary are only included where the terms are used in Annex 2A & B and require further explanation. Definitions, which already exist, have been deemed appropriate.

ATMP Active substance
The active substance of a product is defined in the relevant CTA or MA authorisation dossier. The ATMP active substance is regarded equivalent to an API.

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

Advanced Therapy Medicinal Products (ATMP)
ATMP means any of the following medicinal products for human use:

(a) Gene therapy medicinal product (GTMP):

'GTMP' means a biological medicinal product, which has the following characteristics:

i. It contains an active substance, which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

ii. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Normally GTMPs shall not include vaccines against infectious diseases which would be regulated as per Annex 2B. However, the Competent Authority can make a determination that should follow Annex 2A when this is beneficial and appropriate (e.g. mRNA vaccines that are manufactured using the same platform).

(b) Somatic cell therapy medicinal product:

'Somatic cell therapy medicinal product' means a biological medicinal product, which has the following characteristics:

i. contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

ii. is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a

disease through the pharmacological, immunological or metabolic action of its cells or tissues.

(c) Tissue engineered product:

'Tissue engineered product' means a product that:

i. contains or consists of engineered cells or tissues, and

ii. is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue-engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

i. the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; or

ii. the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

(d) Combined ATMPs:

'Combined ATMP' means an advanced therapy medicinal product that fulfils the following conditions:

i. it must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices, and
ii. its cellular or tissue part must contain viable cells or tissues or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

(e) A product that is classified or determined to be an ATMP by the PIC/S participating authority in its own jurisdiction according to national law.

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

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.

Polyclonal antibodies
Derived from a range of lymphocyte clones, produced in human and animals in response to the epitopes on most 'non-self' molecules

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

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.

Authorised Person
Person recognised by the authority as having the necessary basic scientific and technical background and experience.

Note: For expanded clarity beyond the definition in the PIC/S GMP Guide, the Authorised Person performs certification of batches in line with MA/CTA. After certification, the batches of medicinal products can be released for sale or supply to the market. The Authorised Person has the overall responsibility for release of the products.

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 Process Parameter (CPP)
A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8R2)

Critical Quality Attribute (CQA)
A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8R2)

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)
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. For the purpose of this annex, GMO is intended to cover mutations that are not occurring because of a natural event but are generated by human intervention.

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 either when such materials fail release tests due to the presence of contaminating agent 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 transgenic bank
As above but for transgenic plants or animals.

Master virus seed (MVS)
As above, but in relation to viruses.

Material directly in contact with the ATMP during manufacture and storage
Non exhaustive example list: Processing containers (e.g. fermenters, cell culture flasks and plates, blood bag systems, single use equipment used in automated manufacturing platforms, beads for separation techniques, chromatographic column material), cryo-containers for storage and primary packaging material.

Monosepsis (axenic)
A single organism in culture, which is not contaminated with any other.

Multi-product facility
A facility that manufactures, concurrently or in campaign mode, a range of different ATMPs active substances and products and within which equipment train either 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**.**

Principles of GMP:
The Annex 2A in conjunction with PIC/S GMP guidelines and annexes describes the manufacture of ATMP active substances and ATMP drug products. However, aspects of these guidelines are also relevant for early stages in the ATMP manufacture (e.g. manufcatur of viral vectors, plasmids) where full GMP is not required under national legislation. As a result, the ATMP manufacturer should make sure that all relevant GMP aspects for the manufacturing of those materials are implemented that ensure process control and consistency, investigation of anomalies and control of change.

Processing aids
Substance used in the manufacture of the active substance and medicinal product, which may be present in the finished product e.g. anti-foaming agents, puffer and media additives (salts, pH indicators), enzymes not considered under raw materials

Quality Target Product Profile (QTPP)
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICHQ8R2)

Raw materials
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, and growth factors).

Responsible Person (RP) for blood or tissue establishment
This term is equivalent to the EU term “Responsible Person”. The RP is responsible for the release of the starting material to the ATMP manufacturer. **Blood or tissue establishment:** this term is equivalent to the EU term and for the purpose of this annex is the facility that is authorised according to national law to perform processing (minimal manipulation) of the starting material of human origin.

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 incompetent / devoid
No ability of the vector to replicate.

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.

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

Working transgenic bank (WTB)
As above but for transgenic plants or animals.

Working virus seed (WVS)
As above but in relation to viruses.

Zoonosis (zoonotic)
Animal diseases that can be transmitted to humans.