EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2021
EMA/246400/2021
Inspections, Human Medicines, Pharmacovigilance and Committees Division

Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs

A GMP certificate is not required for manufacturing and testing sites of starting materials for ATMPs. For certain starting materials of biological origin[1], (such as e.g. linear DNA used as template for ex vivo transcription into mRNA, plasmids to generate viral vectors and/or mRNA, and vectors[2]) used to transfer genetic material for the manufacturing of ATMPs it is, however, mandatory that the principles of GMP are complied with.

This Q&A document doesn't set new GMP requirements but it gives guidance on what principles of GMP mean and how to implement them. To this end, a methodology is described to identify minimal requirements in the fields of quality management system, risk management product development, production and quality control to define the principles of GMP applicable to the relevant starting materials.

The assessment of the minimal requirements is performed by the ATMP manufacturer (or, as appropriate, the sponsor or marketing authorisation holder or importer to the European market). The ATMP manufacturer should have access to information about the starting materials that is relevant to ascertain the impact thereof on the quality, safety and efficacy profile of the finished product. To this end, the contract/technical agreement between the supplier of the starting material(s) and the ATMP manufacturer should provide for the transfer of information about the starting material that is relevant to the quality, safety and/or efficacy of the finished product.

In cases where the manufacturer, importer, sponsor and marketing authorisation holder are different legal entities, there should be a written agreement between the parties which lays down the respective duties in this process.

The quality of the starting material is assessed in the context of the assessment of a marketing authorisation/variation application/clinical trial application, and the principles of GMP may be verified during a regular GMP inspection of the ATMP manufacturer.

[1] According to the Directive 2001/83/EC.
[2] Donation, procurement and testing of tissues / cells as starting material are covered by Directive 2004/23 or 2002/98/EC and are not concerned by principles of GMP. They are in consequence not covered by the current Q&A.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

In laying down the principles of GMP applicable to starting materials, it is necessary to recognise a certain level of flexibility for investigational ATMPs based on a risk based approach (RBA), especially in early phases of clinical trials (phase I and phase I/II), due to the often incomplete knowledge about the product as well as the evolving nature of the routines.

1. How are starting materials for ATMPs defined?

ATMP starting materials are defined as all the materials from which the active substance is manufactured or extracted (see Part I of the Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use, paragraph 3.2.1.1 b).

In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells (see Part IV of the Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use paragraph 3.2.1.5).

Donation, procurement and testing of tissues/cells used as starting material are not concerned by principles of GMP but are governed by Directive 2004/23 or 2002/98/EC. When the tissues/cells used are outside the scope of the Directive 2004/23/EC or- as appropriate- Directive 2002/98/EC (e.g. cell-lines/cell banks established outside the EU, or cells procured before the entry into force thereof) section 7.3 of Part IV of the GMP Guide is applicable.

2. What does principles of GMP mean?

GMP requirements for ATMP active substances (drug substances) and ATMP finished products are described in Part IV of the GMP Guide. Some requirements of part IV can also be relevant for the starting materials.

However, the main differences with regard to the starting materials are:

- Not all GMP aspects described in Part IV of the GMP Guide are required.
- According to the current legal framework, neither recurring inspections nor GMP certifications by the responsible authorities are required.

As a result of this situation, the ATMP manufacturers have the responsibility to verify that appropriate GMP requirements are implemented for the manufacturing/testing of the starting materials according to the methodology described in the questions 4 and 5 of the document.

3. When does principles of GMP apply to starting materials used for the manufacturing of ATMPs?

A manufacturing process for an ATMP can be designed in different ways. Consideration should be given to define which manufacturing process steps and quality control testing are applicable to ATMP starting materials, ATMP active substance, or ATMP finished product.

The table below gives examples of where GMP or GMP principles apply in the manufacturing process for ATMPs.

Example Products	**Application of GMP to manufacturing steps is shown in dark grey** **GMP Principles should be applied where shown in light grey** **starting material - active substance - finished product** →				
In vivo gene therapy: mRNA	Plasmid, manufacturing and linearization	In vitro transcription		**mRNA** manufacturing and purification	Formulation, filling
In vivo gene therapy: non-viral vector (e.g. naked DNA)	Plasmid manufacturing	Establishment of bacterial bank (MCB, WCB)		**DNA** Manufacturing fermentation and purification	Formulation, filling
In vivo gene therapy: viral vectors	Plasmid manufacturing	Establishment of a cell bank (MCB, WCB) and virus seeds when applicable		**Vector** Manufacturing and purification	Formulation, filling
Ex-vivo: genetically modified cells[3]	Donation, procurement and testing of tissues / cells[1]	Establishment of a cell bank (MCB, WCB) for plasmid and/or vector expansion and viral seeds when applicable	Plasmid manufacturing, Vector manufacturing	**Genetically modified cells** manufacturing	Formulation, filling

In the table above, the AMTP starting materials are underlined and the ATMP active substances appear in bold.
The construction of the plasmid by in silico and molecular biological methods occurs before the plasmid manufacturing and is considered research and development. Therefore it is not under the scope of the current Q&A.

[3] Ex-vivo genetically-modified cells can be classified as gene therapy medicinal products or somatic cell therapy medicinal products. For medicinal products based on induced pluripotent stem (iPS) cells generated by genetic modification, the principles of GMP shall apply after the procurement of the cells including the generation of iPS cells and the subsequent selection process. (see "Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells EMA/CAT/GTWP/671639/2008 Rev. 1")

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

Figure 1: Example of gene therapy mRNA ATMP manufacturing

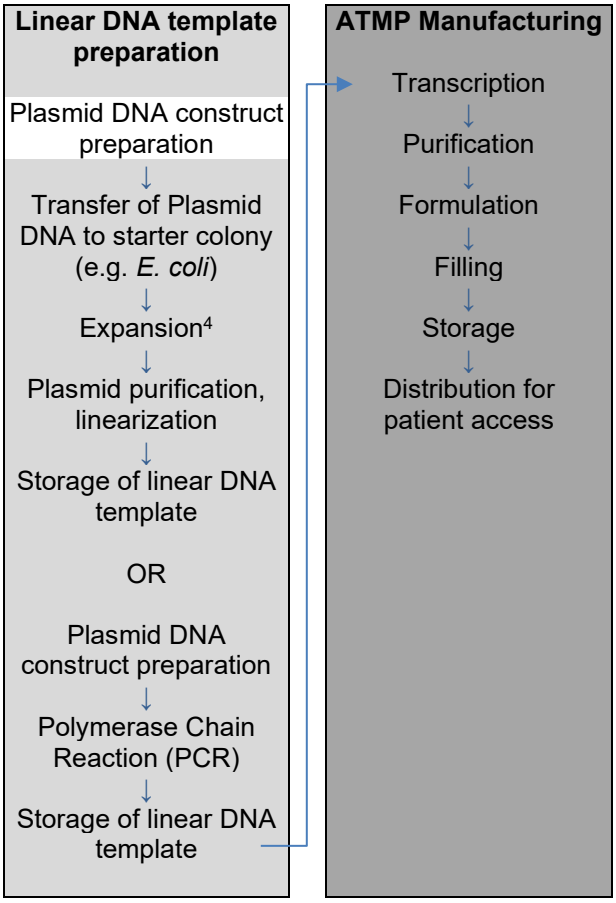
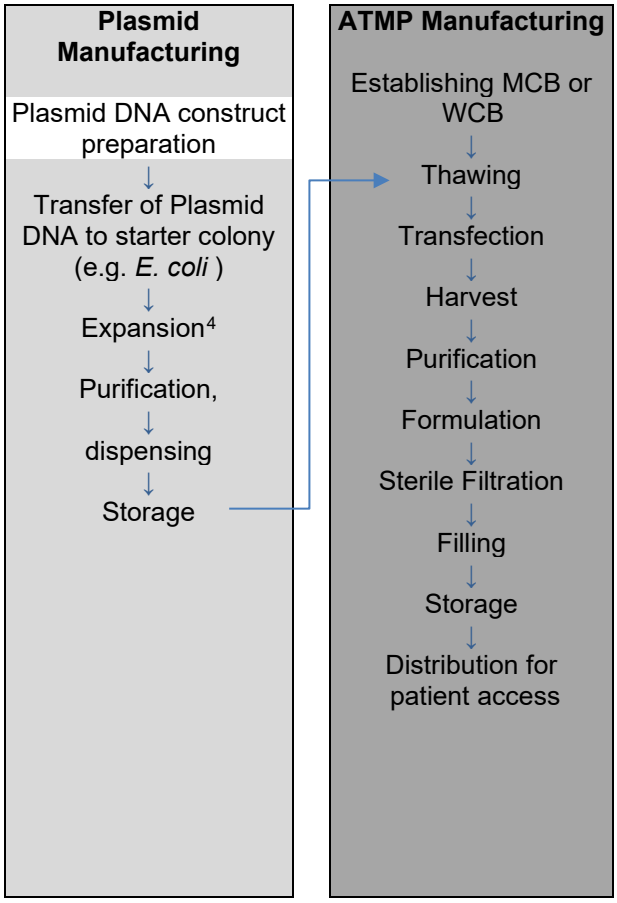
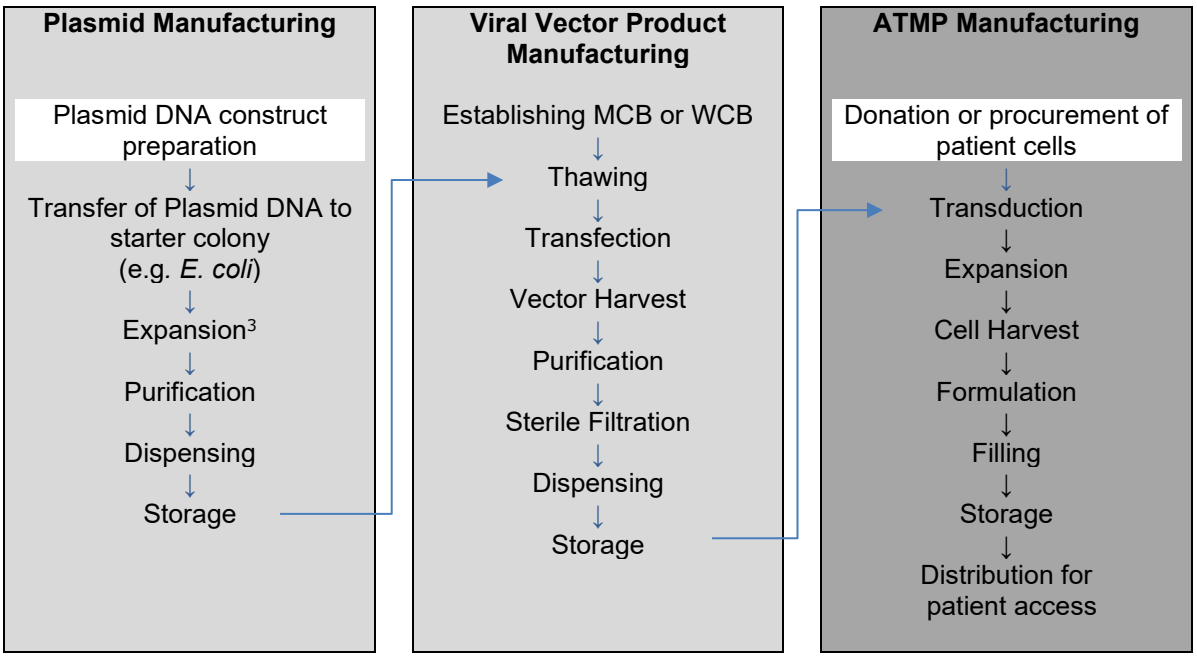


Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing



[4] Establishing a MCB and a WCB might be necessary for this step.

Figure 3: Autologous CAR-T cell therapy ATMP manufacturing



The principles of GMP should be applied where shown in light grey in the above table and figures. Full GMP for ATMPs applies to the areas shown in dark grey.

4. How principles of GMP are defined?

In case that vectors, plasmid and linear DNA template are used as starting materials, the manufacturing thereof should be done in accordance with principles of GMP (light grey area in the table and figures above). In that case:

a) The ATMP manufacturer should apply a risk based approach (RBA) to identify which sections of Part IV of the GMP specific to ATMPs are 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 as explained in question 5.

b) If the starting material is procured from a different manufacturer, appropriate principles of GMP should be determined in the agreement between the ATMP manufacturer and the manufacturer/QC testing site of the relevant starting material. This should cover aspects of the quality management system, documentation, raw materials, cell banks, production, specification, testing and control, storage, and other aspects of handling and distribution as appropriate having regard to the relevant risks for the quality, safety and efficacy of the finished product as explained in Question 5. The extent of the requirements should be proportionate to the potential impact of the starting material in the quality, safety and efficacy of the finished medicinal product.

c) By means of supplier qualification, the ATMP manufacturer should regularly assess if the manufacturer/QC testing site of the starting material has applied the established principles of GMP. The starting material manufacturer is expected to be part of the ATMP manufacturer's supplier qualification program (e.g. questionnaire, incoming starting material QC testing, complains...). A routine audit of the starting material manufacturer/QC testing may be considered to verify the implementation of the agreed principles of GMP.

d) In general, sterile or low bioburden starting materials which can be sterile filtered should follow the relevant requirements laid down in Section 9.5.3 Sterilisation of the Part IV GMP Guideline. Special attention should be given to hold times of specified low bioburden material before sterile filtration and possible microbial growth during this hold time. Otherwise relevant provisions of chapter 9.5 "aseptic manufacturing" of the Part IV GMP guideline should be followed. The manufacturer should justify the applicability extent using a risk based approach (RBA).

5. How does the ATMPs manufacturer ascertain which sections of Part IV of the GMP Guide are relevant for the manufacturing of starting material?

Application of a RBA to starting material manufacturing is a critical part of the process to understand the risks to material quality. For each material used, the risks presented to the quality, safety and function from its source through its incorporation in the finished pharmaceutical dose form must be identified.

Risk factors for consideration should include, but are not limited to:

i. transmissible spongiform encephalopathy;

ii. potential for viral contamination and cross contamination with other vectors or other genetical material;

iii. replication competent virus (in case of replication-deficient viral vector). It should be demonstrated the absence of formation of replication competent virus at the level of the viral production system used[5];

iv. potential for microbiological (e.g. Mycoplasma) or endotoxin/pyrogen contamination;

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

vi. sterility assurance for materials claimed to be sterile;

vii. potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities (for instance residual DNA (antibiotic resistance gene, residual DNA from potentially tumorigenic cell lines etc.), substance of animal origin, antibiotic etc.);

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

ix. stability;

x. supply chain complexity and integrity of packages.

In case that significant risks to the product are identified, measures for risk control and mitigation should be defined and implemented.

6. What are the obligations of the ATMP manufacturer when starting material manufacturing/QC testing site produces also active substances and ATMPs and has a GMP certificate?

The ATMP manufacturer should make an assessment of the quality attributes of the starting material (including relevant aspects of the manufacturing thereof) with a view to ensure the quality, safety and efficacy of the finished product.

[5] See "Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells EMA/CAT/GTWP/671639/2008 Rev. 1"

However the GMP certificate may be considered as part of the risk based assessment by the ATMP manufacturer. It should be assessed which activities of a company are covered by the GMP certificate and which are not. Nevertheless, the ATMP manufacturer must carry out and document the formal risk assessment specific to the starting material in question to determine the principles of GMP to be applied.

7. Is a qualified person required for the production of starting material?

No. A qualified person is not required in connection with the manufacturing of starting materials.