Critical quality attributes for supply of clinical plasmids for cell and gene therapy development

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Abstract

Plasmid DNA is the genetic basis for cell and gene therapy medicines and a sourcing challenge for many innovators. From long-lead times for plasmid manufacturing slots to an evolving regulatory environment, innovators are seeking the highest quality materials that will allow them to meet their timelines. Application of cGMPs to plasmid manufacturing have varied. Fortunately, there have been some recent regulatory publications on this matter – One of the most recent is the EMA 24FEB2021 "Question and Answers document on the principles of GMP for the manufacture of starting materials of biological origin used in to transfer genetic material for the manufacturing of Advanced Therapeutic Medical Products (or ATMPs)". At the most basic level - regardless of how a plasmid is used (as raw material or as an active substance) – the guidance's recommend application of GMP techniques for the manufacturing steps. Some key differences, however, are that in cell and gene therapies as well as mRNA vaccines the plasmid material is regarded as a starting material because the plasmid (code) itself is not considered the active substance. So how is the regulatory guidance evolving for manufacturing of plasmids for cell and gene therapy? The traditional approach is the use a RUO or GMP-like plasmid. GMP-like would refer to the use of the minimum principles of GMP by the EMA Guidance. This GMP-like material would be used for early phase clinical trials. As a therapeutic transitions to later phase clinical trials and commercial launch, full GMP compliant plasmids would be used. The risk in this approach is timeline delays due to transition of raw material needed for GMP manufacturing; potential for inconsistent batches; and risk to clinical efficacy due to changing the manufacturing process of the starting material. An evolving strategy is to start with GMP plasmid early in clinical development to mitigate risk of changes in the plasmid manufacturing process. This allows for consistency in starting material throughout clinical development.

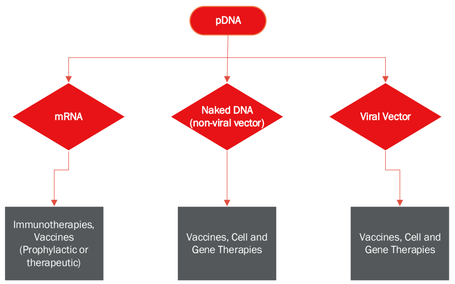
What is not discussed EMA 24FEB2021 the Question and Answers document is the emerging technology of plasmid as a direct in vivo injection (undergoing no mRNA translation to effect the desired cellular change). In this scenario – the plasmid is the active drug substance. This novel therapeutic has the potential to fundamentally shift how plasmid manufacturers are viewed – presently regarded as producers of starting material (and not subject to regulatory inspection) to now being the supplier of the drug substance. Meaning that facilities which are engaged in producing direct inject *in vivo* DS/DP will most likely be subject to regulatory inspection and approval. This is an exciting example where we expect the regulations to adapted to the emergence of a new technology.

Introduction

Plasmid DNA (pDNA)

- Provides coding sequences for cell and gene therapies
- Critical to the supply and success of these products

Applications



Importance of cGMP

Figure 1. Plasmid DNA in viral vector production for gene therapy applications

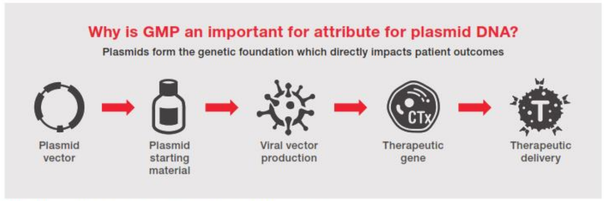


Figure 1: Plasmid DNA in viral vector production for gene therapy applications

Figure 2. EMA recommended standards. February 2021, Q&A guidance addresses plasmid

Example products	Application of GMP to manufacturing steps is shown in blue GMP principles should be applied where shown in yellow 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	Donation, procurement and testing of tissues/cells	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 AMTP 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.

Table 1. Summary of EMA Recommend Standards

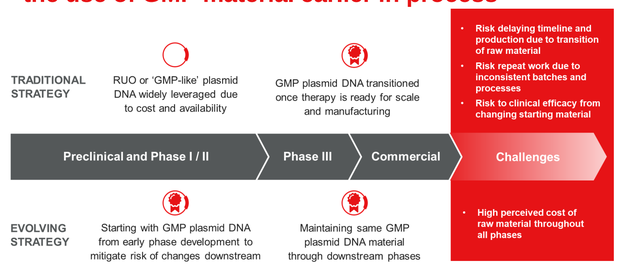
For Advanced Therapy Medicinal Products (ATMP) starting materials, it is mandatory that the principles of GMP are complied with.

- Risk-based approach is utilized
- Manufacture of the active substance and finished product requires use of GMP methods
- Qualification to establish identity, purity, suitability and safety.
- Starting materials must be carefully selected, characterized and qualified for consistent performance.

GMP principles not relevant for starting materials

- No Quality Person (QP) required
- Recurring inspections not required
- GMP certifications are not required

Rapidly evolving regulatory guidance is shifting the use of GMP material earlier in process



U.S. Pharmacopeia recommendations

<1047> Gene Therapy Products

- Summarizes issues and best current practices in manufacturing, testing, and administration of gene therapy products.
- "The quality of raw materials used in the production of a gene therapy product can affect the safety, potency, and purity of the product."

<1043> Ancillary materials (AM) for C,G,&T engineered products

- "To minimize risk to the product, rigorous AM qualification and prudent application of manufacturing process controls are necessary"
- AM quality is critical to GCT product quality and should be qualified by establishing:
  - Identification and sourcing
  - Selection and suitability for use
  - Characterization
  - Vendor qualification
  - QA and control

Application of GMP principles for plasmids

Key practices	How it addresses risk
Quality management system	QU has independent oversight and management of risk.
Material management	Raw materials are appropriate and controlled; Identity of each shipment and traceability to the production batch used

GMP facility, equipment and process	• Prevents contamination and cross-contamination
	  • Clean room technology (Grade A/C, EM, Qualified Operators)
	  • Closed, single use systems, one product per room
	• Production occurs in the same equipment and environment

Master and issued batch records	Defined and repeatable process consistent with development
Deviations, change control, CAPA	Exceptions are evaluated for impact and processes are continually improved
Validated methods (phase appropriate) to release against pre-determined criteria	• Safety methods validated; methods Qualified prior PPQ • Well Characterized Products meeting specifications • CoA and CoC for each batch to document acceptance

Thermo Fisher application of GMP principles using a risk-based approach

1. Applies consistent GMP quality throughout the product lifecycle in order to mitigate risk of changes downstream that could impact safety, efficacy and clinical timelines.
2. Utilizes an FDA/EMA compliant quality management system, which includes;
   1. Material control and management
   2. Process for exceptions (deviations, change control, CAPA)
   3. Document control, including record issuance, reconciliation and retention
   4. Internal and supplier audits
3. Performs aseptic manufacturing in controlled, classified GMP facilities utilizing pre-approved batch documentation based on developed processes
4. Releases well-characterized products only after meeting stringent, pre-approved specifications
5. Supports shelf-life with real time and accelerated stability studies

References

1. FDA Guidance on "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" https://www.fda.gov/media/113760/download
2. EMA 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
3. https://www.ema.europa.eu/en/documents/other/questions-answers-principles-gmp-manufacturing-starting-materials-biological-origin-used-transfer_en.pdf
4. USP<1047>, Gene Therapy Products
5. USP<1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products
6. BioPhorum - Cell and Gene Therapy Critical Starting Material

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