FASTFACTS

How to achieve both cost and quality goals in plasmid manufacturing

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Addressing challenges with plasmid scalability, quality, and production timelines are key to preparing a therapeutic product for commercialization. This poster will showcase key features and quality attributes for GMP Now™ plasmid DNA, and explain how this new option can help in achieving both cost and quality goals in plasmid manufacturing.

DETERMINING PLASMID QUALITY REQUIREMENTS

The growth of cell and gene therapy and the rapid emergence of the mRNA vaccine market have created intense pressure on plasmid DNA (pDNA) manufacturing. A recent industry report indicates the pDNA manufacturing market may see >20% growth by 2030 [1].

Factors involved in determining pDNA quality requirements include the type of plasmid application (e.g., as a raw material or a drug product/substance), and regulatory guidance (considering a specific program's drug designation). Other factors include the project timeline, funding, risk threshold, and internal regulatory feedback.

ADDRESSING AN UNCERTAIN REGULATORY ENVIRONMENT

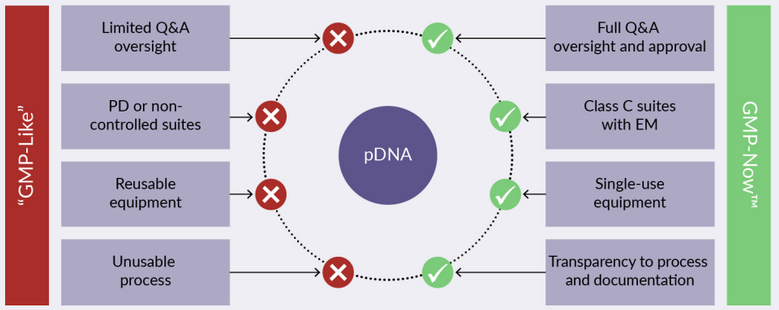
Very little regulatory guidance exists specifically for the manufacture of cGMP raw materials used in cell and gene therapy. Existing guidelines have multiple interpretations and there is a lack of standardization for critical quality attributes and definitions for raw materials. Therefore, pDNA manufacturers must determine the level of controls put in place whilst maintaining a robust supply chain.

Figure 1. EMA recommended standards.

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; 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 substance appear in **bold**. The contruction of the plasmid by an *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.

Figure 2. "GMP-like" vs Thermo Fisher Scientific's GMP-Now™ plasmid DNA.



The European Medicines Agency (EMA) recommendations from February 2021 Q&A guidance specifically address plasmids as starting materials **(Figure 1)**. It is recommended that a risk-based approach is used to determine which GMP principles are applicable to the relevant starting material. The use of GMP quality plasmid material can help mitigate the risk of inconsistent batches, which can increase project cost/timelines and present regulatory challenges.

PHASE-APPROPRIATE PLASMID DNA SOLUTIONS

Thermo Fisher Scientific offers flexible pDNA solutions for use in a wide variety of R&D, clinical, and commercial bioprocessing applications, with scale options ranging from 3 L to 1000 L.

The industry has responded to the lack of regulatory guidance/stringency with a number of different "GMP-like" pDNA offerings **(Figure 2)**. Alternatively, Thermo Fisher is pleased to introduce GMP-Now™ pDNA, produced with full application of cGMP practices and with standard documentation provided. This offers a reduced risk of contamination compared to "GMP-like" pDNA and allows for ease of CMC filing, enabling cost and quality goals in plasmid manufacturing to be achieved.

Additionally, Thermo Fisher Scientific provides cGMP pDNA. This material is also produced with full application of cGMP practices but offers enhanced traceability and/or customized documentation for an additional fee.

More details regarding Thermo Fisher Scientific's phase-appropriate service options are represented in **Table 1**.

Table 1. TFS phase-appropriate options for plasmid DNA manufacturing.

Thermo Fisher Scientific phase-appropriate options	GMP-Now™ plasmid DNA (early phase)	cGMP plasmid DNA (early phase–commercial)
Pass-through cost included	●	Estimate provided
Calibrated and qualified equipment	●	●
Produced using Thermo Fisher plasmid platform process	●	●
Produced under full quality oversight	●	●
Produced using quality approved master batch records	●	●
Batches tested using qualified platform methods	●	●
Production in monitored GMP Class C controlled suites	●	●
Produced from MCB	●	●
Client specifications for custom plasmids	●	●
CoA, CoC, TSE/BSE statement provided at release	●	●
Cross contamination control with single-use equipment	●	●
Client audits supported		●
Access to QC raw data		●
Tech transfer custom processes available		●
Process optimization and validation available		●
Executed batch records provided		●
Regulatory support for 3.2.S.2.3		●
Client-specific method qualification/validation		●
Client approval on documentation		●

REFERENCE

1. Plasmid DNA Manufacturing To See Impressive Growth In Years Ahead.

CELL & GENE THERAPY INSIGHTS

Cell & Gene Therapy Insights 2023; 9(8), 1087; DOI: 10.18609/cgti.2023.142

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