

TO GMP OR NOT TO GMP? THAT IS THE (PLASMID) QUESTION

By Eric Gudorf, Director of Client Services, and Erika Morris, Director of Business Development

As gene therapies continue to stake their foothold on the clinical trial landscape and comprise the future wave of lifesaving pharmaceuticals, high-quality GMP-grade plasmids are increasingly in demand as critical raw materials. Since their use in gene therapy production is still relatively new, health authority regulation around plasmids can be limited, and due to the demand and costs associated with their manufacturing, GMP-grade plasmid suppliers often have finite capacity.

As drug manufacturers work to secure plasmids for discovery, clinical, and commercial applications, the question looms: how can you maintain a manageable budget while procuring a high-quality plasmid supply? Though opting to begin with a GMP-grade plasmid platform – as opposed to GMP-lite – may initially seem the more expensive route, this strategy offers long-term benefits, including cost savings and a consistent raw material supply.

The Why and How of Plasmids for Gene Therapy

Plasmids are small structures of double-stranded DNA that became popular genetic therapy vehicles thanks to their ability to deliver high amounts of DNA. Historically, plasmids have been used to manufacture non-commercial DNA vaccines for government-funded programs and early-phase clinical studies. Prior to the gene therapy boom, there wasn't high demand or widely available capacity for plasmid production. However, once they were identified as vital raw materials for viral vectors, demand for GMP-grade plasmids skyrocketed.

Frequently when manufacturing gene therapies, multiple plasmids are required as starting raw materials. For example, with adeno-associated viral vectors (AAVs), three different plasmids commonly must be manufactured: an AAV plasmid, a helper plasmid, and a plasmid carrying the gene of interest. Once produced, all three plasmids are transfected into mammalian cells and further processed to develop a gene therapy drug product. The need to run multiple production campaigns to obtain sufficient plasmid raw

material often requires numerous slots of a CDMO's capacity; as a result, any available plasmid production spaces could be highly coveted. Ultimately, though, it is crucial to partner with an experienced plasmid manufacturer with the capability to produce GMP-grade plasmids that will mitigate risk.

De-Risking Your Plasmid Process with GMP-Grade Manufacturing

GMP-grade plasmids yield a variety of benefits, including more extensive traceability of raw materials, higher quality oversight, and higher-grade production suites for manufacturing. When you work with a supplier that has a proven GMP platform and robust quality system in place, all necessary documentation is ready to go, allowing your plasmid to be rapidly onboarded. GMP processes leverage platform technologies with consistent performance and predictable results. If there is an issue with a specific plasmid and platform technology, a process development team will identify it during testing and implement process improvements to accomplish ideal yields and recoveries. A GMP-grade manufacturer will conduct repeated quality control checks utilizing platform assays to ensure high-quality, reproducible results, including but not limited to a high percentage of supercoiled, low endotoxin, and low residual host cell DNA and protein. Upon release of a GMP-grade plasmid, your team will receive a full certificate of compliance and a certificate of analysis for quality control testing.

Though the number of plasmid suppliers is growing, many opt to run GMP-lite programs to cut client costs or host quality systems that are still in development.

While a new manufacturer may have never released GMP-grade plasmid before, some experienced plasmid manufacturers have been producing GMP-grade plasmids for over two decades. Established partners have also mastered their approach to production space and resource usage, placing them in a position to offer benefits like high-efficiency throughput.

As regulatory guidance continues to evolve, it is highly beneficial to work with a CDMO that has previously conducted plasmid production processes that were tested and deemed FDA-compliant. Currently, the FDA views plasmids as critical gene therapy raw materials and recommends the documentation of all design, manufacturing, and purification procedures as well as testing to assess purity, and identity.¹ Plasmids have a unique designation since they will be further modified prior to human introduction.

Beyond quality control and platform efficiency, a high commitment to transparency and collaboration further secures the plasmid production process. A CDMO

should be willing to tailor their approach to your needs, be that working directly with an alliance management team or a more hands-on project design. Ideally, they will provide a dedicated project manager throughout the lifespan of your project that can help ensure all parties are continually engaged in open communication. As the client, you should have the opportunity to provide feedback on all documentation, including batch records and any quality events or investigations.

A Vital Partnership

A strong relationship with your plasmid partner stems from clear expectations about your ideal plasmid product and the ability of the supplier to sufficiently interpret those expectations thanks to experience, plasmid knowledge, and high-quality GMP-grade platforms. As you navigate obstacles together, ideally each party communicates their needs to find solutions and reach a shared goal. Even though the project belongs to your team, the right CDMO should be equally invested in the flourishing of your drug program and will provide high-quality plasmids to help ensure the success of your drug product.

Resources

1. U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. *Chemistry, Manufacturing, and Control (CMC) information for human gene therapy investigational new drug applications (2020)*. Rockville, MD.

About the Authors

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About Ajinomoto Bio-Pharma Services

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