In-House Plasmid Production to Secure Supply Chains

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Plasmid DNA represents a crucial component of many cell and gene therapies. Plasmids, which provide the coding sequences that facilitate viral vector production for therapies ranging from mRNA vaccines to bespoke cell therapies, have experienced a surge in demand in recent years, in concert with the proliferation of new and promising biologics in the development pipeline.

Securing the plasmid supply chain for a project hinges on a number of factors, and because the number of plasmid suppliers is still limited when contrasted with demand, finding a contract development and manufacturing organization (CDMO) partner with the requisite expertise, external supply chain, and capacity can seem a daunting prospect. Two of the primary drivers impacting plasmid manufacturing are time and quality: long lead times for materials, as well as variable regulatory standards and phase-specific criteria surrounding the manufacture of plasmids, have created uncertainty for developers and manufacturers across the space. Combined with the historically high costs of plasmid production, these challenges can serve to delay and derail projects without proper planning and partnering strategies.

Circumventing some of the insecurity surrounding the plasmid supply chain requires creative solutions and strategic partnering. A CDMO with in-house plasmid manufacturing capabilities can help companies accelerate timelines and ensure material availability, ultimately saving time and money throughout their product life cycle.

The Challenges of Plasmid Sourcing

The cell and gene therapy space is always evolving – the requirements for research and GMP-grade plasmids alike are sure to change in the future, though whether these are bound to become more stringent or more relaxed is uncertain. This consideration, coupled with the cost of producing plasmids, has galvanized a movement across the field to innovate in order to lower the burden of plasmid production. For many, the tightening regulatory landscape has proven challenging, forcing many to adapt their manufacturing approaches to accommodate evolving expectations surrounding plasmid quality at various stages of production. Additionally, the current capacity for plasmid production has been outstripped by demand, creating long lead times and contributing to the perception that delays in plasmid procurement are largely insurmountable.

Three primary types of plasmid DNA are currently produced for cell and gene therapy applications: research-, clinical-, and commercial-grade. Within these categories exists additional nuance; for commercial-grade plasmids intended to serve as raw materials, the regulatory standards are much less stringent than for plasmids selected to serve as active pharmaceutical ingredients (APIs). That stringency is even greater for plasmids that function as a finished product. These varying degrees of regulatory stringency, depending on a plasmid's intended use, result in increased cost and time constraints for companies working toward return on investment. Moreover, there are also variations in plasmid design that can have both regulatory and performance implications. These design elements can range from plasmid backbone size and selectable markers (i.e., antibiotic resistance) to regulatory sequences and functional cDNAs and more. Moving forward with sub-optimal plasmids often results in reduced performance, functionality, and regulatory issues in the finished product. When compounded with the stringencies described above, this can be disastrous for any program. Finding a plasmid supplier that has expertise in plasmid design and is able to support a project's vertical integration from early research grade through toxicology, clinical manufacturing, and commercialization is paramount to ensuring its success.

Overcoming plasmid procurement delays is crucial for companies whose early clinical programs rely heavily on data access and agility to bring promising drugs to the clinic. Currently, many of these companies rely on CDMOs that, in turn, rely on one or two of the largest plasmid manufacturers, forfeiting much of their supply chain control in the process. Even companies that source their own plasmid often find themselves contending with long lead times; finding a CDMO that can manage both plasmid and vector has the potential to mitigate this uncertainty, streamlining sourcing and creating a seamless transition from plasmid production through vector development all the way into commercial manufacturing.

This approach also serves to greatly simplify coordination and qualification for a program; managing activities between two CDMOs can be a difficult task, as can qualifying each. Ensuring that multiple manufacturing partners have the systems in place to meet regulatory requirements, as well as the capacity to produce the necessary materials and the data to support quality control, ultimately becomes a duplicative effort, one that can fail if either party is

fundamentally misaligned with the program in question. This can be particularly risky when it comes to identifying a plasmid manufacturer, as many CDMOs are relatively new entrants in the plasmid production space. Finding a partner with the track record, data, and internal expertise to de-risk a program that relies on plasmids means taking a holistic look at a CDMO's experience in the space, as well as its recent investment and ongoing efforts to innovate its plasmid production paradigm.

Finding the Right Partner to Avoid Supply Chain Pitfalls

Access to plasmid is a significant stumbling block in downstream biopharmaceutical manufacturing; instability in manufacturing, as well as issues identified post-sequencing, are perhaps bigger factors in this problem than capacity, but all are important considerations for companies looking to streamline their development efforts. Working closely with a CDMO that performs in-house plasmid production affords companies the opportunity to collaborate and optimize processes and create efficiencies. Housing plasmid manufacturing and product manufacturing under the same roof is one distinct advantage of partnering with a CDMO capable of producing plasmids. Another is working with a partner willing to work closely with clients to improve yields, maximize quality, and streamline operations for the life cycle of a product.

Partnering with a plasmid supplier that can scale alongside a therapy's development can save companies time and money through standardized, connected protocols, comprehensive data aggregation, and in-house expertise. Andelyn Biosciences, a pioneering biopharmaceutical CDMO with capabilities that span plasmid production, viral vector analytical development, small- and large-scale adherent and suspension GMP drug substance manufacturing, and finished drug product manufacturing, has invested years of research to optimize its plasmid production capabilities. By prioritizing cross-functional communication and utilizing an enterprise resource planning system supported by frequent demand meetings, Andelyn works to ensure material availability and adequate safety stock.

But ensuring that timelines are maintained and materials are available goes beyond supply assurance – delivering the right product is critical to maintaining the trajectory of a program. With more than 25 years of experience with viral vector manufacturing and more than a decade of plasmid experience, Andelyn offers customers access to unparalleled troubleshooting and characterization expertise. Its current plasmid offerings include research and tox-grade plasmids, with experience in more than 75 clinical trials globally and plans to expand its capability to GMP-grade plasmid production. Andelyn's advanced quality systems, full regulatory support, and supply chain vertical integration make it a valuable partner for companies regardless of phase or complexity.

With a wealth of experience identifying and achieving the critical quality attributes necessary to optimize plasmid production, Andelyn can help companies ensure that their upstream activities are aligned to support their downstream program goals. Prioritizing plasmid production is critical, as poor plasmid design can lead to a range of issues, from inverted terminal repeats (ITRs) integrity to partial transgene packaging and everything in between. A wide variety of factors energetically, stoichiomet-

rically, and chemically impact this design, so having a CDMO partner that can facilitate a project's vertical integration from early research grade through toxicology, clinical manufacturing, and commercialization is paramount to ensuring its success.

Ultimately, Andelyn is working toward eliminating its reliance on external plasmid suppliers completely, fomenting a system around capacity housed entirely internally, with five new production suites ranging from individual shake flasks to 200-liter fermenters. This push complements its recent investment in a new 185,000-square-foot facility in Columbus, Ohio dedicated to commercial-scale cGMP gene therapy production. These investments are crucial in a space where every drug product starts with DNA – as the foundation of many of the drugs currently in development in the cell and gene therapy space, plasmid DNA is core to the future of the advanced therapy industry as a whole.

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