

— OPTIMIZING PLASMID PRODUCTION STRATEGIES & PARTNERSHIPS —

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As an array of new plasmid providers enter the biopharmaceutical market to meet demand, drug sponsors must navigate varying levels of manufacturing skill and choose wisely. In the search for a plasmid partner, you may wonder whether to prioritize the lowest sticker price, the most immediate capacity for production, or previous plasmid production experience. To find the best fit for your plasmid, there are several key factors to consider, including whether to produce good manufacturing practice (GMP)-grade material from the start. As you explore potential manufacturing partners, consider the offerings necessary to manufacture your plasmid with quality and efficiency, including process knowledge and streamlined project teams.

Prioritize Plasmid Experience

An experienced plasmid manufacturing team will have an established understanding of how to manage their capacity, i.e., the number of projects their team and facilities can support. Particularly, they will have the skills to facilitate stretch goals as clients are onboarded to ensure critical timelines are met and maintained. Without a high level of capacity management understanding, a CDMO could overcommit.

As manufacturers aim to maintain timelines, they must also be aware of lead times, which continue to be an issue in the post-COVID marketplace. During early discussions with a CDMO, even during the business development phase, examine how timeline expectations are managed. Are they proposing realistic or overly aggressive timelines? Are they willing to push back if a client's expectations may be too aggressive? Furthermore, the CDMO must understand what is needed to release plasmid material. If not, they may produce the plasmid within the promised timeline but struggle to release it, and thus, fail to meet the timeline.

In the instance that bottlenecks do arise, accomplished CDMOs have proven strategies to address them. With process familiarity, a CDMO gains knowledge of the consistency and yield they will achieve from each fermentation. They'll be able to plan for sufficient materials, account for long lead times, and avoid ordering in excess. This will de-risk the process to guarantee the amount of plasmid needed in the appropriate number of batches. Again, a seasoned partner will understand appropriate scale-up estimates and plan accordingly to yield major cost savings and avoid project overrun.

Seek Out Streamlined Project Teams

With experiential knowledge comes better team integration to support your needs. A plasmid production platform entails upstream and downstream processes. The upstream phase includes fermentation and cell harvest, while downstream goes through to purification. These moving parts necessitate collaboration to ensure a smooth project execution and on-time delivery.

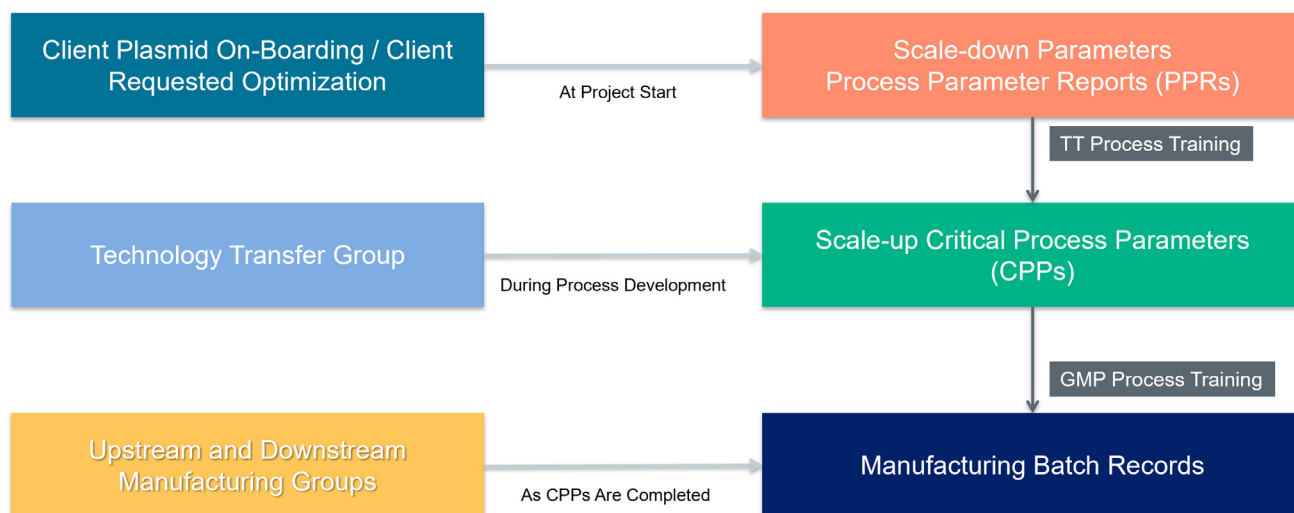


Fig. 1 – Technology transfer information flow

The fermentation team will need to review their optimized media composition and determine how to achieve high cell densities as well as their feed strategy. Once they produce as much cell mass as possible, they will need to identify how to recover it efficiently for maximum recovery. During the purification phase, an established platform won't need significant optimization, but chromatography steps will need to maximize efficiency. Thus, the work that was completed by the upstream team will be captured in the downstream work. Along the way, in-process analytical testing will be conducted.

With the upstream and downstream teams, there is a flow of technology information as clients transfer knowledge to the CDMO (Figure 1). At the project start, there will be onboarding between the client and manufacturer, and a client may request optimization. From there, the CDMO may consider scaled-down parameters to accomplish the tech transfer at a smaller scale. The technology transfer group will be present for process development, optimization, and setting scale-up critical process parameters correctly. Once these steps are complete, GMP

process training for manufacturing batch records begins. It is an iterative process between client and CDMO as they determine the critical parameters and achieve smooth tech transfer.

Any delays could be detrimental to patient access and successful market launches. The integrated project teams across the platform provide continuous timeline communication and corrections as needed. For example, if the upstream team has delays in production, they collaborate with the downstream team to make up for it. These teams offer a streamlined project progression with appropriate team overlap and shared knowledge.

For the success of an integrated project team, it is critical to have a central project manager as a dedicated point of contact to facilitate reliable communication between the client and project team SMEs to ensure timeline delivery. With an experienced CDMO, a project manager will have gone through multiple client programs and thus know how to manage the process skillfully. As the project progresses, you will continue to build rapport, and

if problems do arise, you will be comfortable having an open discussion to make sure the scope of the project stays on track.

Choose GMP From The Start

Plasmids are typically considered critical raw materials for emerging cell and gene therapy modalities like adeno-associated virus (AAV) and lentivirus. As a result of the growing market need, there has been an explosion of plasmid providers, some GMP-based and some not. In the case of startup plasmid producers, many begin with phase-appropriate pDNA production and add GMP components as clients reach that stage. In this system, you are building your GMP production and release system while running a plasmid production business, which doesn't allow for focused GMP oversight from the very beginning. In many of these projects, multiple plasmids are required. To accommodate them, companies may offer off-the-shelf plasmids that may or may not have been produced as part of a GMP process. If multiple production runs are needed to produce sufficient plasmid and there is no existing GMP system, you run the risk of production runs with inconsistent quality attributes and yield that could impact the final product.

Alternately, with GMP-based plasmid manufacturing, robust GMP programs are in place from the very beginning. In terms of long-term benefits, a GMP manufacturer offers raw material traceability and consistent quality and supply of raw material that allow for reproducible plasmid results. Quality oversight will be in place from the outset, from raw materials to production and release. GMP-grade manufacturing suites are generally higher grade, controlled spaces that offer efficient processes and reduce the risk of background issues.

By starting with a GMP supplier, uniform plasmid production will be secured via GMP oversight. With this kind of consistency, clients could realize cost savings in terms of reproducibility. A proven GMP quality system tests materials at release for any issues and anticipates obstacles throughout the process. If a CDMO offers platform GMP technologies, you will have access to rapid onboarding and high-efficiency throughput. This increases their capacity and allows plasmids to be produced at a much higher rate while maintaining predictable results and leveraging multiple quality checks. If a problem does arise, the quality system will deter-

mine where it occurred and address it with minimal timeline and product impact.

Avoid The Common Pitfalls Of Plasmid Production

It is also critical to be cognizant of the common risks associated with plasmid manufacturing to help ensure that your team avoids timely and costly delays. Timeline management is essential, particularly for new programs aiming to be first to market. Consider if a CDMO has a safety stock of long lead items. Without one, project start times could be significantly delayed. Templated batch records will also support the timeline, ensuring that the client doesn't have to wait for a batch record to be created each time and that process operators are adept at performing them.

Communication is another vital component. As you evaluate CDMOs, assess their communication style from the very beginning. Prioritize working with an enthusiastic team that responds quickly and thoughtfully and expect initial communications to reflect later ones. First, consider how long it takes a CDMO to respond to your initial inquiry. From there, they should set expectations transparently and deliver on what is promised. A good project team will adjust their communication style to match what the client needs and the cadence of the project rather than using a one-size-fits-all approach.

It is critical to verify that a CDMO has the capabilities to keep a client within their budget. As you review project proposal details, consider how the project costs are laid out:

- Are all components captured?
- Is there a discussion of potential cost overruns?
- Is the CDMO being open about potential added costs?
- Do they provide a line-item estimate of those materials, and do they have reasonable overage to make sure that the client isn't going to spend more than they expect?

Even though plasmid production is relatively straightforward, there are nuances that require experienced subject matter experts. As you are meeting with a CDMO, make sure their knowledge matches the project requirement. If your plasmid

is larger or more difficult to manufacture, determine if they have the right SMEs to address it. They should also have on-site SMEs to provide analytical and quality support. A quality team should conduct ongoing testing throughout upstream and downstream production to catch any issues. This quality function must have the oversight and experience to release a high-quality product in a timely manner.

The Bottom Line

The partner you choose for your plasmid production will influence your timeline, costs, and product quality. While some may promise the fastest production timeline or the lowest bottom line, ultimately, choosing a knowledgeable GMP-grade plasmid manufacturer will de-risk your process and provide a high-quality product when you need it most.

About Ajinomoto Bio-Pharma Services

Ajinomoto Bio-Pharma Services is a fully integrated CDMO with sites in the US, Belgium, Japan, and India, providing comprehensive development, cGMP manufacturing, and aseptic fill finish services for small to large molecule APIs and intermediates. Our San Diego site was founded on plasmid manufacturing and offers over 25 years of experience, 17 independent suites, and GMP production scale-up from 100 L and 1,000 L fermentation vessels. We are dedicated to quality in our drug substance and drug product platforms and provide a high level of service to meet our clients' needs. To learn more, visit our website: <http://www.ajibio-pharma.com/>.