EXPERIC

Making Key Decisions for Efficient and Cost-Effective Biopharmaceutical Drug Development Programs

By: Sheetal Muley, Ph.D., Senior Director, Research & Development, Experic;
Daniel Kestyus, Scientist, Technical Operations, Experic

Introduction

In today's biopharmaceutical landscape, financial markets are tighter while speed to market remains a critical factor when making development decisions. Increasingly, biopharmaceutical companies are having to make tough choices when prioritizing development of investigational products in their pipelines. Working with a contract development and manufacturing organization (CDMO), however, can help stakeholders ensure that the design of a product's development program is efficient and appropriate for the stage/phase of development. This article will address how a biopharmaceutical company can leverage the collaborative efforts with their CMDO partner to understand the implications of certain key development decisions. We will also discuss a few types of decisions companies may want to avoid which may preserve cash or reduce costs in the short term but can have unwelcome effects later.

The Case for Risk Assessments

The drug development landscape is incredibly competitive, and biopharmaceutical companies are feeling the increased need to accelerate development programs. This need for efficiency may be linked to several factors, such as a start date for a clinical trial, a press release date, funding preservation, or an upcoming Investigational New Drug (IND) filing deadline. With this immense pressure to move quickly comes a strong temptation to defer certain activities during the drug development process. However, these perceived short-term efficiencies that are meant to expedite timelines may adversely impact the achievement of longer-term goals, potentially causing future delays and resulting in additional expense.

To avoid these types of surprises, a risk assessment is recommended at the outset of any drug development project so both the biopharmaceutical company and the CDMO can clearly delineate and discuss risks versus benefits of potentially deferring certain development activities. Working together, they can assess what information is available and how much additional information is required for the sponsor to be confident that the drug product is developed appropriately, and the manufacturing process is robust. A variety of scenarios can be evaluated during such risk assessment(s) to determine the best path forward and produce the most successful outcomes.

During each risk assessment, it is important to differentiate between critical and noncritical processes. Discussions should ideally begin before the project is onboarded with the CDMO. The biopharmaceutical company will be best served by sharing all relevant background information with the CDMO, including previous successes and failures in clinical studies, technical challenges, developmental challenges, formulation issues, and analytical methods.

Working together, the CDMO and the biopharmaceutical company can acquire a solid understanding of the specific product development needs and requirements, paying special attention to technical challenges and timelines. This allows the CDMO to work with their client to strategize in a very targeted way to customize the development strategy to the biopharmaceutical company's specific needs.

There is no cookie-cutter approach to processes in drug development. Consider a product that is in an early phase of development and is moving into Phase I proof-of-concept studies. Here, there is much more flexibility from a CMC regulatory perspective, resulting in a simpler product development approach. In contrast, a product that is in late-stage development approaching an NDA submission will require far greater diligence in product development and a large number of studies may be required to ensure that the drug product formulation and manufacturing processes are robust and in control. Active pharmaceutical ingredient (API) characteristics play a major role in drug product performance attributes, and it is imperative to identify these characteristics early on so the CDMO and biopharmaceutical company can determine appropriate product development strategies.

The Importance of Early API Characterization

A well-characterized API provides the "jumping off point" for a robust drug product development program. API characterization should be performed early to establish predictive measures for a product's performance, processability, and stability. If the product is a formulation, the compatibility of all excipients must also be verified. In this case, conducting a compatibility study initially in the project is critical to confirm the choice of excipients. Having an accurate understanding of the material at the beginning of the study can shave time off the development process.

Preformulation studies are a key part of the characterization process and are especially important when the API is classified as Biopharmaceutics Classification System (BCS) class II or class IV due to poor solubility. Development of drug products containing poorly soluble APIs requires use of appropriate formulation-enabling technologies to ensure that the drug is well absorbed and the systemic exposure of the drug is satisfactory. Preformulation studies provide all the information needed to pinpoint the optimal strategy for leveraging formulation-enabling technologies. While any number of approaches might improve the solubility of the API, the optimal approach will keep the product stable, facilitate robust manufacturing, and provide consistent *in vivo* exposure from early phase development to clinical stage and beyond. When a company minimizes or overlooks preformulation studies to preserve resources early in development, there can be unintended consequences. For example, a chemical or physical instability in the API or lack of consistent *in vivo* exposure can become evident six to twelve months into development. At that point, the company may need to redevelop the drug product to either improve stability or to improve its *in vitro* or *in vivo* performance which can consume significant time and additional financial resources.

Conquering the Challenges of Transitioning From Research & Development to GMP Manufacturing

Biopharmaceutical companies face additional challenges when a drug product progresses from R&D to the GMP manufacturing stage. Partnering with a CDMO early in the drug development process can streamline this process significantly. When engaged early, the CDMO can customize the development program to manufacture an R&D feasibility batch to identify the most important quality attributes for the formulation and determine process parameters. This approach smooths the transition between the R&D and GMP manufacturing.

On the other hand, when a biopharmaceutical company has performed the R&D work internally and then uses a CDMO for clinical batch manufacturing, technical transfer activities are involved in making the transition. Here, the availability of the biopharmaceutical company's comprehensive technology transfer

package can improve efficiency. Ideally, the package will contain all information about the API, excipient compatibility, basic formulation development, and any challenges that may have been previously encountered. The tech-transfer package should also contain any analytical methods developed so that appropriate verification can be performed at the CDMO. With this data, the CDMO can conduct small-scale feasibility batches to ensure replication of what was done previously and fine-tune the manufacturing process parameters. Once the feasibility batches are complete, the CDMO team will have a thorough understanding of the formulation and manufacturing process and will have confirmed that all operations are performing as designed and expected. The drug product is then ready to be moved into clinical batch manufacturing.

Potential challenges can occur when the biopharmaceutical company has an expectation that the clinical batches will yield the same results as the process parameters used during R&D batches, especially when very few R&D batches have been manufactured at small-scale and scale-up needs to be conducted during clinical batch manufacture. Critical process parameters may need to be adjusted or optimized during scale-up to avoid unexpected issues during GMP manufacturing. It is imperative that intermediary scale batches (also called demo batches, which are usually simulations of clinical batches) are manufactured prior to clinical batches to evaluate processing parameters and environmental factors that might affect outcomes.

The need for intermediary scale batches is especially relevant in the manufacture of certain difficult-to-handle powder formulations. Biopharmaceutical companies that have conducted R&D studies with positive outcomes and acceptable product characteristics may believe a manufacturing process has been optimized. If the powder/intermediate material properties have been satisfactorily characterized during initial R&D studies, any challenges occurring during scale-up/clinical batch manufacturing may be readily resolved. If material attributes have not been adequately understood before venturing into larger scale clinical batch manufacture, additional troubleshooting of the manufacturing process, analytical testing, and process optimization will become a necessity to achieve the biopharmaceutical company's requirements for product quality and yield.

Selecting the Right CDMO Partner

Given the challenges outlined above, it becomes obvious that a biopharmaceutical company that outsources product development should select a CDMO partner carefully. It is important to consider the following factors: technical expertise, a thorough understanding of the relevant regulatory requirements, available technology, flexibility, and a collaborative approach.

Technical expertise is a major consideration for CDMO selection. When vetting potential CDMO partners, biopharmaceutical companies will want to speak directly with members of the technical team, posing careful questions that help gauge the level of knowledge and technical depth. These discussions usually occur after a confidentiality or nondisclosure agreement is signed, so there should be comfort on both sides to share information. The right CDMO partner will have the expertise and technology to challenge the process, evaluate worst case scenarios, evaluate extremes, and anticipate challenges that might occur during scale-up. They can even predict the behavior of the materials and how a batch will perform during manufacturing having considered existing external environmental conditions. Additionally, a thorough site visit is essential to fully evaluate a CDMO's capabilities, technology, and level of expertise.

Beyond technical expertise and technology, the right CDMO partner will have up-to-date and specific knowledge and expertise on the current regulatory landscape. Each project will demand adherence to different guidelines and requirements depending on the type of drug product and the proposed indication. Given the frequency of updates to regulations across various markets around the globe, the importance of being "regulatory savvy" cannot be overstated.

Flexibility is imperative during process development as it allows the CDMO to take rapid corrective actions

when unexpected challenges arise. An example is the significant variation in fill weight that can occur during manufacture of second or third clinical batch campaigns due to variations in the lot-to-lot density or particle size distribution of the API or the excipients. It is vital to react quickly to address these challenges before scaling up manufacturing. Smaller biopharmaceutical companies who rely on CDMOs for product development capabilities have reported that the lack of flexibility of a CDMO partner can become especially obvious during the execution of R&D/feasibility studies.

Another key consideration is the extent to which the CDMO takes a collaborative stance when working with the biopharmaceutical company. A successful relationship should include transparent communications and a level of trust from both parties, and the right CDMO partner should feel a vested interest in the biopharmaceutical company's victories and take full ownership and accountability for their contributions to the product development process. The CDMO project team should be transparent about any issues with the manufacturing process, equipment, or resources and immediately communicate those challenges to the sponsor with a mitigation plan. Finding a CDMO that works closely with biopharmaceutical companies is the key to having smooth, streamlined product development processes from the earliest evaluation to the commercial stage.

Experic prides itself on technical expertise, exceptional flexibility, collaborative approach, technology savviness, and knowledge of regulatory requirements. The CDMO has invested in significant resources and has expertise in various types of formulation-enabling technologies, including technologies for challenging, novel, high-potency compounds, and has significant experience in dry powder inhalation products. In addition to development, manufacturing, and analytical capabilities, their clinical packaging team is available to seamlessly manage primary packaging, secondary packaging, kitting, storage, and clinical distribution. Experic remains focused on increasing its capabilities and services by incorporating only the best talent, equipment, and processes to ensure clients receive the exceptional services needed for their biopharmaceutical projects.

Conclusion

Today's drug development landscape can lead to a significant temptation to aggressively reduce costs and save time during drug development. While aiming for efficient and cost-effective programs, these decisions can be shortsighted. A well-characterized API, robust technical transfer package, preformulation studies, and phase appropriate risk assessments can create a sound foundation on which to base a development program and establish predictive measures for critical quality attributes including drug product manufacturability, solubility, and bioavailability. A flexible and collaborative CDMO partner with the relevant expertise, technology, and regulatory knowledge can support these risk mitigation strategies and efficiently and cost-effectively deliver phase appropriate development programs.

EXPERICSERVICES.COM • 609.537.4040 • 888.397.9733 (toll free) • info@expericservices.com • 2 Clarke Drive, Cranbury, NJ 08512