Lonza
Biologics

Overcome Challenges And Secure Successful Technology Transfers Of Complex Biological Products In Sterile Manufacturing

Angela Armanni, Senior Director, Global Head MSAT, Drug Product Services, Lonza

The biopharmaceutical industry has seen many challenges in the last few years, spawned not just by a global pandemic but also the industry-wide disruption of operational and supply chain strategies that emerged in its aftermath. Now, as pipelines continue to fill with complex new modalities, more manufacturers are turning to CDMOs to take advantage of cutting-edge technologies, advanced expertise, and available capacity that can improve their response time in the face of changing market trends. As a result, the pool of CDMO options is growing, intensifying the need by manufacturers to better understand the checklist of qualities and capabilities they'll need their next partner to possess.

One critical area to consider is their ability to successfully complete technology transfers, which involves an intricate set of activities and disciplines that, if done incorrectly, could result in delays and failures that impact the overall success of your end product. Recognizing what it takes to complete this process effectively and efficiently is crucial to selecting the best partner for your project and product needs.

Tech Transfers During Sterile Drug Product Manufacturing

The development and manufacture of new and innovative biopharmaceutical products of a certain complexity, e.g., biological products, mRNA vaccines, antibody drug conjugates (ADCs), and others, remain challenging and require a wide range of advanced technical and scientific competencies. Multiple requirements for both sterile manufacturing, storage, analytical testing, and further characterization are necessary to preserve the final quality of the drug product. Therefore, a tech transfer includes the exchange of all product and process knowledge required to successfully support progression from product development to clinical trials and, ultimately, commercialization. This process takes place between either development and manufacturing within the same facility or between two different facilities, sometimes in different geographical locations, which may pose some challenges.

Regardless of the development phase of the product, though, a tech transfer may appear as a simple task founded on the basic principles of transferring product knowledge from the originator (sending unit) to the recipient(s) (receiving unit), creating documentation, and enabling production of the drug product at the final designated manufacturing line. In reality, the tech transfer for drug products can be a complicated operation and calls on the successful completion of many interconnected activities, whose complexity intensifies as the scope of the tech transfer increases, inevitably requiring several manufacturing and product changes. In fact, rarely does a tech transfer occur without any change from the sending unit to the receiving unit. Varying factors that can affect the ease of the transfer include, but are not limited to, whether the facility is single or multi-site; if the transfer is only drug product related or if it is an integrated transfer of drug substance and drug product; or if the transfer is limited only to manufacturing or if it includes a broader scope of activities, including analytics, assembling devices, etc. Nevertheless, a CDMO with knowledge of multiproduct production will be able to navigate and overcome these challenges using established processes and technical expertise.

The need to undertake a technology transfer is initially required at the beginning of the drug product life cycle, when transferring the product and its corresponding manufacturing process from development laboratories to the GMP production line at the designated manufacturer (internally within the sponsor company or externally at a CDMO). This is typically for clinical drug product supplies corresponding to investigational new drug (IND) and/or investigational medicinal product dossier (IMPD) submission.

Subsequently, within the continued life cycle of the drug product, additional technology transfers may need to be performed for other reasons, such as during:

- biological license application (BLA) programs to prepare for commercialization, e.g., transfer to a final CMO supporting late-phase clinical programs, regulatory approval, commercial launches, and routine manufacturing;

- scale-up due to company business expansion or strategic business continuity; conversely, there may be a need for small, customized batch size requiring optimized process losses and manufacturing process improvements (typical for advanced therapeutics, such as a gene or cell therapy, which operate at a smaller scale and unit);

- drug product presentation optimization, e.g., lyophilized to liquid form to facilitate and improve the use of medication for more patient-centric administration, such as changing from a lyophilized vial to liquid vial and preferably to a prefilled syringe; or

- post-approval regulatory variations as part of overall drug product process improvement, e.g., moving from legacy into new, state-of-the-art isolator filling systems with minimal manual interventions that necessitate more stringent GMP and regulatory compliance.

Often, a combination of reasons applies, leading to complex technology transfers with multiple changes. Every manufacturing and technical product change shall be carefully addressed for its corresponding impact to product quality, which shall be preserved and eventually confirmed by successful demonstrated comparability of the new transferred product with the original pre-transferred one.

Successful comparability is ultimately necessary to meet GMP and regulatory requirements, thereby minimizing regulatory hurdles connected to technical transfer approval by health authorities.

Overall, it is best to minimize changes between the sending and receiving units during tech transfers in order to increase the likelihood of success. However, this is not always possible, as it is rare that a tech transfer is executed without changes, especially if there are site changes, scale-up, new technology, etc.

The Importance Of Knowledge Transfer

Because of the numerous types of information exchanged during a tech transfer, they often involve many different stakeholders and experts of diverse biopharmaceutical backgrounds who possess high levels of scientific, technical, and quality skills as well as a thorough understanding of regulatory expectations and pathways. The involvement of a cross-functional technical team is essential for tech transfers, as flexibility and a wide range of capabilities are needed to accommodate customization and improvements that may be necessary based on the biopharmaceutical drug product's complexity as well as its development and manufacturing requirements. The unique characteristics of some biologics, particularly new modalities, can increase the inherent complexity of tech transfers due to their heightened sensitivity.

For example, new modalities like mRNA drug products command critical storage conditions and can present a challenging supply chain, as there is currently limited access to GMP-grade raw materials for mRNA manufacturing as well as uncertainty about the most appropriate container closure system combination to preserve container closure integrity at frozen conditions throughout the drug products shelf life. Other drug products, like ADCs, require specialized technical and scientific competencies as well as enhanced containment solutions to prevent cross-contamination and ensure personnel safety. Likewise, gene therapy products also have varying requirements, such as GMP-quality requirements for BSL-2 when operating in a shared drug product facility. Overall, multiple requirements for sterile manufacturing, storage,

and analytical testing and further characterization are necessary to preserve the final quality of the drug product.

Because of these factors and more, it is imperative that the sending unit provides sufficient clarity about the unique needs of the product to be transferred to the receiving unit, as this helps progress it into the facility fit assessment and define the extent of the scope of the transfer, e.g., investment requirements, that may be necessary for initial clinical manufacturing. When considerable investments are required or modification is needed to the established platform processes at the receiving unit, it is important at this initial stage of the tech transfer to clarify not only the initial clinical needs but also any requirements for later commercialization. Knowing these needs ahead of time allows for proactive planning that ensures the most efficient and cost-effective approach to development and manufacture and also helps avoid unnecessary and costly delays later on. It is important that all parties familiarize themselves with the roles and responsibilities of those involved in the core business, which may be especially crucial in a complex organization structure.

Recognizing the importance of strong project governance, we at Lonza Drug Product Services (DPS) provide a dedicated technical transfer lead paired to a dedicated project manager for every technical transfer to secure both adherence to milestone progression as well as in-depth technical knowledge exchange between the cross-functional project teams. By doing so, we can facilitate and secure constant and robust information sharing and foster open and transparent communication to the customer, covering all required technical details necessary to support in-depth knowledge transfer during the initial phase as well as smooth progression during the execution phase of the transfer till final closeout.

Overall, we conduct technical transfers using a systematic, holistic approach that relies on detailed gap assessments for the manufacturing process as well as analytical methods performed during the knowledge transfer phase at the beginning of the tech transfer. We conduct a comprehensive comparison of:

- all drug product components, such as excipients, and direct product contact materials, e.g., primary packaging and equipment, including consumables;
- drug manufacturing processes for each unit operation; and
- analytical testing for in-process control and quality control release and stability of the finished product, including extended product characterization and required innovative analytical techniques.

Risks to product quality from the identified gaps are addressed by identification of the most appropriate mitigation actions based on our extensive, overall biological product database on both DS and DP, experience in manufacturing and capabilities, and ad hoc, tailor-made development studies.

The Importance Of On-Site Visits

All key stakeholders in the project, such as the tech transfer lead, the project manager, and all subject matter experts (SMEs), should be involved with planning from the very beginning. This also includes regulatory and quality experts. While their expertise is typically not needed at this early stage, it is essential to foster the relationships and interactions of these experts on each side to avoid misunderstandings later when the project is underway in GMP manufacturing. Additionally, it is highly recommended that all parties meet on-site at the CDMO prior to the transfer. This not only allows the customer to conduct face-to-face meetings with the team assigned to their project and strengthen the working relationship across SMEs from the beginning, but it also facilitates a capabilities audit to evaluate the facility and its equipment as well as the procedures and processes of the team utilizing them.

In addition, it is beneficial that a CDMO has the opportunity to visit the customer's site, especially if the transfer involves a commercial product, which requires several regulatory binding aspects that can constitute constraints (and preferably should not be changed) during the tech transfer. By visiting the, the CDMO team can witness the execution of the commercial batch, which provides clear insight into what needs to be transferred in detail on a process level and helps define the overall transferability of the asset into the receiving unit manufacturing line at the fill-and-finish site.

We encourage on-site visits at our facilities as well as our customers' facilities to increase the chance of success of the tech transfer by observing the product manufacturing in real time, see the facility fit assessment beyond what is outlined on paper documentation, and clarify technical needs, such as whether platform assets and processes should be adjusted or to what extent a possible customization is required to fit the product being transferred. In this regard, we act as a CDMO with the flexibility and agility necessary to accommodate changes when needed. These characteristics are crucial to driving biologics production and meeting timelines in an increasingly competitive market.

A Holistic Approach To Tech Transfers

Cross-functional interfaces during a tech transfer can pose many challenges and often create attrition, due to product knowledge gaps, lack of information sharing and/or product understanding, or even differing intercompany policies and functionality. While capabilities and expertise weigh heavily when selecting a CDMO, experience is especially paramount when it comes to tech transfers. It provides the critical foresight necessary to identify potential issues before they occur, supported by processes and procedures that can help safely launch a customer's product in the market.

With several years of experience in manufacturing not only monoclonal antibodies but also many types of complex mole-

cules, Lonza DPS offers the experience, expertise, and manufacturing capabilities for handling and producing a variety of biological innovative products in drug product manufacturing in different dosage forms. This includes large batch as well as small batch manufacturing, making it an ideal partner for producing large molecule drug product therapeutics for varying types of customers. Lonza DPS capabilities extend from pharmaceutical development to analytics, with the most sophisticated and state-of-the-art innovative technologies to meet the more stringent requirements of new modality product types as well as to manufacture equipment and processes at fill-and-finish GMP plants, including regulatory experience with multiple health authorities. Our technical experts possess the profound scientific knowledge necessary to deeply understand the drug product. This includes every aspect related to the product quality profile, the history of the product, its stability and major criticalities, the manufacturing process to be transferred, and GMP and regulatory requirements.

Our passionate and highly dedicated teams have successfully transferred multiple customer processes at our GMP fill-and-finish lines of a wide variety of biological products, making us a leader in the industry when it comes to technology transfer activities.

The diversity and complexity of today's biologics call on many different types of disciplines when it comes to their development and manufacture, including during the tech transfer process. However, while people play a critical role in the path to market, so too does technology. As pharmaceutical manufacturers rely more and more on outsourcing partners, it becomes the responsibility of CDMOs to invest in innovative technologies that can serve the needs of customers and their products. Yet, for those with an expansive global network, it is also important to ensure the technologies and platforms they utilize are harmonized from site to site to facilitate transferability. That is why we have established comparable or equal assets across all units from laboratory to pilot to clinical and commercial scale to sufficiently support the buildup of strong platform processes, which then supports the smooth transfer of the process and product from one site to the other. These assets facilitate the process parameter setting as well as allowing prediction of product behavior upon exposure to manufacturing and production conditions. This setup also minimizes changes and the need for additional studies as well as the need for post-approval regulatory variations, thus increasing the success rate of a transfer, especially for complex products.

A CDMO For The Future

Well-prepared and positioned CDMOs serve as a fierce advantage in a biopharmaceutical market that continues to grow and change. Therefore, outsourcing partners must operate with their fingers constantly on the pulse of the industry in order to appropriately adjust and expand their capabilities to provide technically sound services at scale. We focus on continued learning and growth by applying a lessons learned methodology both internally and externally. This includes collecting feedback from our SMEs as well as our customers, breaking down the inherent silos in development and manufacturing in order to increase awareness and drive continuous improvement. We have also invested heavily in capacity, with well over a billion dollars of expansions announced in the last two years, as well as continuing to invest in talent.

This additional capacity and talent are crucial in our ongoing efforts to build on our vast experience that backs our growing customer base. In 2022 alone, we supported more than 600 preclinical and clinical large molecules and over 55 commercial large molecules. This includes mammalian, microbial, cell and gene therapy products, and bioconjugates. Approximately 30% of these molecules had expedited review designations. In our commitment to quality, innovation, and patient care, we are constantly implementing new ways to accelerate our customers' path to the clinic and to the market.

At Lonza, we pride ourselves on the high level of expertise and experience within our network. These resources are vital for not only overcoming the many challenges of tech transfers but also providing consistently high-quality products in the scalable way needed to meet the changing demands of today's unpredictable but exciting market.

04.2023.1