FACILITATING TECH TRANSFER FOR PARENTERAL PRODUCTS

→ BY **MARGA VIÑES**, GRIFOLS PARTNERSHIP

Pharmaceutical outsourcing by definition requires the transfer of technology from the sponsor company to the service provider. Outsourcing of sterile injectable fill-finish projects brings additional complexities and risk. Successful tech transfer in these cases requires a CDMO with extensive process and product understanding, a comprehensive quality culture, and the willingness of both parties to form true collaborations based on trust.

TECHNOLOGY TRANSFER DEFINED

The goal of technology transfer according to ICH Q10 is to "transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization." This knowledge "forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."[1]

Meanwhile, pharmaceutical technology transfer, according to the Parenteral Drug Association, "consists of planned and controlled actions that are based on well-defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as a sending unit (SU), to a new site, the receiving unit (RU)."[2]

The World Health Organization focuses on controls for transfer of processes along with the necessary documentation and professional expertise: "Technology transfer embodies both the transfer of documentation and the demonstrated ability of the RU to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and any applicable regulatory bodies."[3]

What does all of this actually mean for a sponsor company looking to outsource parenteral drug product fill-finish activities? Strong alignment between the sponsor and CDMO is crucial. The service provider should not only have the physical capabilities – facilities and equipment for manufacturing, sampling and analysis – plus sourcing and technology transfer management systems and various control strategies, but also extensive process and product understanding, a risk-based approach (quality by design) and a culture that both allows for flexibility and is founded on a commitment to quality and trust. In other words, the ideal CDMO must act as an extension of the sponsor and serve as a partner, not simply a supplier.

A FOUNDATION OF TRUST

The more knowledge that a sponsor company shares about the process to be transferred – and the product to be manufactured using that process – the more smoothly tech transfer can be accomplished. Of course, sharing this type of proprietary knowledge carries risks. Sponsor companies should carefully select a CDMO with which they can build an intense, two-way relationship, thus establishing a level of real trust.

Lack of information can have significant, negative consequences for the technology transfer process. Not only does it typically lengthen project time lines, it creates additional work for the CDMO, adds to customer cost, and can potentially have safety consequences for plant personnel and even the patient. Confidentiality agreements between sponsors and CDMOs should help circumvent this issue, as they are designed to protect both parties.

CDMOs with excellent track records of performance, such as Grifols Partnership, have no interest in misusing information or taking any actions that will negatively impact their reputations. Because a large part of our business is in blood derivatives, a market in which success is driven largely by reputation, we are committed to maintaining highly positive perceptions of the Grifols name in all markets that the company participates in.

LEADS TO DEEP COLLABORATION

Establishing a strong foundation of trust not only facilitates technology transfer through greater knowledge sharing, it also leads to the development of much closer relationships between the sponsor and CDMO, which in turn results in deeper collaborations that further enhance the technology transfer process.

Collaboration is also enabled at Grifols by the use of an integrated project management strategy. Cross-functional teams with representatives from all relevant areas – manufacturing, R&D, quality assurance, quality control, regulatory as well as sales and marketing – report to team leaders with expertise in technology transfer and extensive experience within the company. Such a collaborative effort between Grifols and our customer allows for consideration of all potential consequences before implementation of even the smallest changes. The result is the avoidance of unexpected problems and the need to make corrections. Such an effective team also makes it possible to readily resolve any problems that do arise, preventing unwanted delays and keeping projects on schedule.

UNDERSTANDING ON MANY LEVELS

The need for understanding is not limited to the process and product that are being transferred. Knowledge of each party's expectations and limitations is essential. Familiarity with project management and quality systems at both companies can also facilitate rapid completion of tech transfer projects.

Although not often considered during technology transfer, an understanding of the market and the needs and expectations of the ultimate end user can also be highly beneficial to this important process. CDMOs with knowledge of patient preferences and an understanding of how even small changes in process or product design might impact final product acceptance can help guide the tech transfer process towards a more positive outcome. Indeed, bringing patient/physician/caregiver considerations into the development process as early as possible can significantly influence the success of a tech transfer program.

QUALITY MATTERS

A culture of quality and effective quality systems are essential to successful technology transfer, particularly for the production of complex products such as sterile injectables. In order to participate in the plasma-derived proteins market, Grifols has made an extensive commitment to quality. Quality culture is at the roots of our company and it branches out to all of our businesses, including our sterile fill-finish operations.

Perhaps most notably, Grifols has never experienced any quality problems with its blood derivative products due to virus contamination. Also indicative of our robust quality systems is the fact that we received zero 483 complaints following our most recent (June 2015) FDA audit. It is also worth noting that Grifols was one of the first companies in Europe to obtain approval for the parametric release of parenteral solutions in glass and flexible containers from its manufacturing plants in Spain. Parametric release is authorized

for companies that have shown a sterility assurance release program that has demonstrated a control of the sterilization process and high consistency in their overall quality system.

The company has also invested heavily in automation technologies to reduce the risk of error and contamination for increased operator and patient safety. For instance, our "Form-Fill-Seal" technology – implemented for the production of polypropylene bags – and our fully automated glass vial filling lines both minimize human interactions with drug products. Artificial vision systems (developed in collaboration with Diagnostic Grifols), which enable the automatic inspection of injectable products for particulates, also eradicate the potential for human error.

DEEP RESOURCES BRING BENEFITS

Technology transfer is a complex, multistep process requiring the input of teams of experts at both the sponsor and CDMO levels. Access to resources that can simplify the process, provide improved process controls and/or facilitate communication and collaboration can be highly beneficial.

As part of a successful, global pharmaceutical manufacturer, Grifols Partnership has access to a depth of resources not available to stand-alone CDMOs. Financial resources can be available for investment in new technologies, capacity and/or capabilities required for technology transfer projects. In addition, the equipment used for contract manufacturing projects is the same equipment used for internal Grifols production, so operators have intimate knowledge of their performance characteristics.

This equipment is designed specifically for Grifols by Grifols Engineering, a Grifols company devoted to the design of pharmaceutical production plants, processes and machinery. This vertical integration allows Grifols to be as independent from suppliers as possible. It extends, as mentioned above, to the Form-Fill-Seal technology for filling PP bags. Most importantly, vertical integration enables Grifols to control the entire process, ensuring achievement of the highest quality.

CONCLUSION

Technology transfer is integral to pharmaceutical manufacturing. Whether a process is being transferred from one site to another within a company or between a sponsor and an outsourcing partner, success requires extensive knowledge sharing and real collaboration between the sending and receiving teams. While transfer to a CDMO can potentially carry additional risk, selection of a service provider with extensive experience in tech transfer, a robust quality culture and a commitment to collaboration can in fact facilitate the tech transfer process.

For companies looking to outsource sterile injectable fill-finish operations, including the development and manufacturing of products that require advanced technologies and complex production processes, Grifols is just such a CDMO. We focus on the sterile fill-finish of small-molecule intravenous solutions. Approximately 70% of incoming projects are direct tech transfers, with the remainder also involving process/formulation development. We work with customers from early stages of development through commercial manufacturing and provide scale-up and tech transfer of processes, including process development and validation, engineering runs and clinical and commercial batches, analytical method development and validation, stability studies, dossier support documentation, and labeling and packaging in glass and plastic vials, glass bottles and flexible PP bags. P

Regarding trust and understanding customer needs, we would like to highlight a recent customer agreement

A certain company is looking for a new CMO for a product because the current CMO has decided not to continue manufacturing an IV solution.

The project faces different challenges:

- The product is the only product in the portfolio of the company.
- Current product stock is insufficient to cover the expected market demand over the next two years.
- Market demand for the product is increasing at a healthy rate.
- Exhibit batches should be submitted to FDA six months after the signing of the agreement.

Moreover, the customer does not have the analytical protocols available or the manufacturing flow chart. This information is not provided by the current CMO. Based on its experience and knowledge of intravenous solutions, Grifols decides to go ahead with the project. In order to accomplish the narrow time line, we need to define alternative actions for any possible setbacks and ensure a thorough control of the technology transfer stages. Grifols decided to prioritize the project prior to handling internal projects and allocated additional human resources to those initially anticipated; this is an example of our commitment towards customers.

REFERENCES

1. *ICH Harmonized Tripartite Guideline:* Pharmaceutical Quality System Q10. Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 4 June 2008. Web.
2. *Technology Transfer: Technical Report No. 65.* Rep. Parenteral Drug Association. Web.
3. *WHO guidelines on transfer of technology in pharmaceutical manufacturing.* Rep. World Health Organization. Web.

GNL-CM-2400003

ABOUT THE AUTHOR

Marga Viñes
Business Development Manager, Grifols Partnership

Marga Viñes holds a degree in pharmacy and an MBA in pharmaceutical management from the University of Barcelona. She has more than 15 years' sales and marketing experience in the pharmaceutical industry and healthcare business, defining and implementing marketing strategies for international and domestic markets. In addition, she has nine years' experience in the field of strategic marketing and business development in the contract manufacturing business on an international level.

LinkedIn www.linkedin.com/in/marga-viñes-a9aa748
Email marga.vines@grifols.com