ROUNDTABLE REPORT

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Biologics Development, Manufacturing & Packaging Roundtable

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KEY TAKEAWAYS

- Biologics are more complex to manufacture, package, store and distribute than other dosage forms with the newer biologics being more complex than the first wave.
- Biologics manufacturing is experiencing short- and long-term capacity challenges as companies focus attention and resources on COVID-19 treatments and vaccines.
- To mitigate drug development risks and reduce time and costs through commercialization, Life Sciences companies employ a variety of strategies.
- Common hurdles in partnerships relate to product packaging, supply chains, clinical trials and regulatory policies.
- When selecting a partner to handle packaging operations, communication and the partnership between sponsor company and CDMO is as important as capabilities.

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OVERVIEW

Biologics are a unique class of pharmaceuticals with many complex requirements when it comes to developing, manufacturing, packaging, storage and distribution. The often strict thermal requirements of drug substance and subsequent drug product means the life cycle management from clinical phases through to commercial launch poses significant challenges requiring specific expertise. When outsourcing any aspect of the supply chain, success depends on both sponsors and vendors operating as a true partnership with both sides understanding the requirements relating to all aspects of the supply chain. Strong, collaborative relationships and clear communication are the hallmarks of robust sponsor-CDMO relationships.

CONTEXT

A panel of experts from PCI Pharma Services and three Life Sciences companies discussed challenges and opportunities related to the development, clinical phases and commercialization of biologics. They offered insights on how to improve sponsor-CDMO relationships.

KEY TAKEAWAYS

Biologics are more complex to manufacture, package, store and distribute than other dosage forms with the newer biologics being more complex than the first wave.

The panelists shared their experiences working with biologics:

- **Thermal stability is often an issue.** Some products such as live vaccines and next generation biologicals may need refrigerated and frozen storage conditions. In some cases, products need to be packaged for shipment with extra precautions, such as crush readings to prevent damage and absorbent pads in the event of vial breakage.
- **Managing the logistics of biologics during the early stages of clinical trials can be difficult.** Challenges can arise in terms of shelf life management due to the complexity of packaging required. Obtaining the permits and declarations to ship early-stage biologics is also challenging when safety and SDS information is limited.
- **The drug format may introduce challenges for end users.** Biologics such as bispecifics, fusion proteins and cell and gene therapies can be much less stable than some of the older more 'straightforward' monoclonal antibodies and may be manufactured as lyophilized powders requiring complex reconstitution and mixing by the end user. This may be a concern when the end user is the patient rather than a healthcare professional and so the entire supply chain is more complex and needs careful consideration.
- **The longer-term storage requirements may be different to ongoing storage and distribution requirements.** Some biologics for example may have long-term bulk storage conditions of -70 degrees Celsius, but then distribution to the end user may be between 2 and 8 degrees Celsius. This adds to the overall complexity of the supply chain — especially at larger scales — as paperwork must accurately account for the end user temperature, which is different to the storage conditions while in the facility.
- **Packaging of cold chain biologics can be challenging and expensive.** If a product is stored in frozen conditions and is then, for example, moved to ambient conditions for packaging, additional

complications can arise. Close monitoring of the product from a quality perspective is required, including time out of refrigeration to validate any process. This in turn adds to the overall cost as when testing the product there is the cost of the device itself, plus the often very expensive drug product used during this process, so being mindful of any process defects is essential.

- **Devices used to administer biologics tend to be expensive.** Unlike other pharmaceutical products, biologics are often packaged in the more patient-centric prefilled syringes or auto injector formats which can be more costly.

Biologics manufacturing is experiencing short- and long-term effects due to the COVID-19 pandemic.

In the commercialization of biologics, the pandemic has created multiple manufacturing and supply chain challenges. COVID-19 vaccine production has consumed manufacturing capacity at many CDMOs and pharmaceutical companies.

In addition, nearly every aspect of the supply chain has been stressed. Companies are struggling to find raw materials, consumables like vials and analytical materials. Early in the pandemic, PCI Pharma Services helped partner manufacturers obtain raw materials and stored inventory on their behalf.

> The supply chain has definitely been stressed by COVID-19. One of the things we learned is that if you go far enough down the supply chain, every business is essential. Even basic supplies are dictating the ability to deliver on some more advanced platforms.
>
> *Alex Weaver, PCI Pharma Services*

Temperature-controlled shipping boxes for biologics are also now in short supply. Since shipping container manufacturers are also experiencing supply chain challenges, lead times for these items can be months. As many patients are now receiving medications directly to their homes, demand for temperature-controlled containers has increased, which is further exacerbating container shortages. From a transportation perspective, commercial flights were drastically reduced during the pandemic. PCI Pharma Services, for example, is now using standard courier cargo flights to move products.

> Affordability of biologics is a real challenge and this will be further exacerbated due to the pressures on healthcare from COVID-19. We need smart innovation that not only improve patients' lives, but is also affordable to enable broad access. We can do this by efficiencies in discovery and product development for new therapeutics and also by using novel technologies to enhance existing products, which is where Arecor for example is focused. Looking ahead, I think affordability will remain one of the biggest issues facing biologics.
>
> *Sarah Howell, Arecor*

Looking ahead, the affordability of biologics will continue to be an issue. Despite the supply chain-related challenges caused by COVID-19, some positive developments have emerged. Examples include:

- **Increased technology adoption.** Over the last 18 months, there has been an unprecedented uptake in Life Sciences of new technologies such as use of artificial intelligence.
- **Greater innovation.** Companies are reexamining how to develop and ship products that patients can self-administer and safely store at home.
- **More regulatory flexibility.** During the pandemic, rules and regulations became much more flexible. The pharmaceutical industry has shown it can do things differently, while maintaining safety and data integrity. PCI Pharma Services, for example, participated in remote Qualified Person releases. Time will tell whether regulators will return to a more regimented approach.

To mitigate drug development risks and reduce time and costs through commercialization, Life Sciences companies employ a variety of strategies.

The roundtable participants shared several ways their companies are addressing challenges associated with the current drug development environment:

- **Developability assessments.** In its work on novel molecules, Crescendo Biologics is developing new expression and purification methods. As a result, the company cannot rely on decades-old platform technologies. The team conducts robust developability assessments to ensure that molecules are able to withstand expression and purification stresses, as well as any cold chain issues that may arise during the product life cycle.
- **Early evaluation of stability data.** To address issues that may occur during shipment, PCI Pharma Services provides sponsors as much upfront data as possible related to stability, freeze/thaw conditions and temperature range excursions. Many companies do not generate this type of data because it is costly and many teams do not consider it at the outset of a project.
- **Testing with multiple excipients.** Valneva tests its drugs with several different excipients. This reduces uncertainty and risk during the product life cycle.
- **Improving existing products.** Arecor is leveraging technology to improve existing pharmaceutical products like insulin. Since the base product is already approved, the development pathway is abbreviated. Although clinical studies are needed to show that products are superior, the company does not need to conduct the full suite of studies needed for novel biologics. This results in more affordable products that can genuinely improve patients' lives and achieve a faster time to market.
- **Working more efficiently.** COVID-19 has proven that it is possible to expedite timelines and reduce red tape in order to get life-saving medicines into the hands of those who need it. Process Failure Mode Effects Analysis for multiple products running on the same line is time consuming and excessive. It is time to look at how we can eliminate redundant aspects of the supply chain and prioritize crucial analysis, reducing both timelines and the cost of medication for patients.

> We are working on novel Humabody™ molecules and we can't rely on decades-old platform technologies. That adds complexity to the CMC picture. We conduct robust developability assessments, to ensure that molecules can withstand expression and purification stresses, as well as cold chain issues.
>
> *Richard Williams, Crescendo Biologics*

Common hurdles in CMC partnerships relate to product packaging, supply chains and clinical trials.

The panelists reflected on their partnerships and identified three common issues:

1. Packaging formats. Many contract manufacturers have a finite number of ultra-low temperature freezers with racks and boxes designed to fit a certain vial size. When drug development companies select a different size vial, custom racks and boxes are needed which in turn may slow product shipments. To try to negate this, PCI Pharma Services runs client packaging designs through simulations to optimize storage and shipping costs as much as possible.
2. Nonstandard temperature bands. When products don't conform to standard temperature ranges, contract manufacturers often have to obtain special containers and equipment that can be hard to find. In addition, some countries don't have the transportation infrastructure to maintain product temperatures with shipments waiting on hot airport tarmac until clearing customs. To reduce that risk, Valneva is looking at transporting products by ship in sealed containers that can maintain -70 degrees Celsius. Although maritime is slower than air transportation, it is being explored as a potentially lower risk option.

> If the temperature band for shipping products is nonstandard, the size of containers and equipment can be a problem. Shipping systems aren't always the limiter, however. It can be airports that have no storage facilities for products that are waiting to clear customs.
>
> *Rich Nelson, PCI Pharma Services*

3. Clinical trial participants. Even prior to the pandemic, there was considerable competition to recruit patients for some trials such as those in oncology and this situation has worsened with COVID-19.
4. Differences in regulatory policies among customers. Following the launch of a product, and as more data becomes available, changes may be required with regard to packaging process. Such changes could be as simple as moving the process to a different room to increase volumes and optimize efficiency, which can be a relatively simple solution. In some such instances, these changes may be embraced by companies with little to no disruption. Sometimes, however, the opposite can be true — causing major delays in the project that can be months or even years — while the small change needed goes through a potentially unnecessary extensive regulatory approval.
5. Differences in the evaluation of a change. Different companies may approach a required change with the same process irrespective of the actual change. For example, evaluating a change to a fill-finish process compared to, for example, a change to a labeling process after the API is protected by its packaging, should really be evaluated with two different lenses. One process could potentially impact the drug product, the other cannot. By considering this, changes to the commercial packaging process could be streamlined, reducing timelines and ultimately cutting costs for both the client and end user. It really comes down to a calculation of risk versus benefit, however, this can vary drastically from company to company making it difficult to gauge and get ahead of.

When selecting a partner to handle packaging operations, best practices can lead to successful collaborations.

Session participants identified three best practices that lead to more successful partnerships between Life Sciences companies and contract manufacturers:

1. **Try to work with one partner for the entire product life cycle.** Ideally, stay with the same partner throughout the product journey, since it can be painful to move between CDMOs. If you need to change, go back to your shortlist of selected CDMOs and evaluate them again.
2. **Define 'must have' and 'nice to have' criteria for partnerships.** When Valneva evaluates partners, the team creates a project scope document outlining 'must haves' and 'nice to have' criteria. Valneva shares this document with several potential partners. Laizé noted that the company doesn't select partners solely on technical capabilities. It also values communication skills and the strength of the relationship.

> It's important to be as transparent as possible and to make partners feel involved in the project. We are looking for proactive partners who will collaborate. We want CDMOs that will challenge the process and recommend improvements.
>
> *Julien Laizé, Valneva*

3. **Educate CDMO employees about the product.** Prior to the pandemic, PCI Pharma Services routinely invited clients to employee quarterly meetings to discuss their products. This gave staff members a greater sense of purpose and an understanding of how their work affects people's lives. Williams commented that he spends time educating CDMO employees about his company's product so they aren't "just filling a glass vial with a colorless liquid".

> We see sponsors with all different levels of experience with biologics. Some clients are new to the field and they're very cautious. They may have unusual storage temperatures that won't work for stability long term. We look at different ways of doing things and try to support them in the best way possible.
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> *Rachel Griffiths, PCI Pharma Services*

BIOGRAPHIES

Rachel Griffiths

Associate Director, Technical Services, PCI Pharma Services

Rachel joined the company in 2004 and has held leadership roles in Operations and Technical Support. Her current role involves overseeing the installation and validation of new facilities at the company's Bridgend site and the implementation of new technologies and innovations in controlled-temperature packaging, storage and distribution services. With a degree in Microbiology and Virology, Rachel is the Biological Safety Officer for the Bridgend site and also has previous experience as a development scientist, a technical support scientist and a product support specialist.

Sarah Howell

Chief Executive Officer, Arecor

Sarah was appointed Chief Executive Officer of Arecor in 2015 having joined in 2011 as Chief Operating Officer and Executive Director. During her time at Arecor she has led the transformation of the business into a successful clinical stage biotechnology company. Sarah has a background in clinical and commercial pharmaceutical product development, manufacture, supply and licensing across a range of product types and therapeutic areas. She has served in a number of senior roles in the pharmaceutical industry, including Vice President CMC & Technical Development at BTG Plc., and Director of Outsourced Manufacturing at UCB-Celltech. Sarah holds a BSc in Chemistry from the University of Birmingham and a Ph.D. in Physical Organic Chemistry from the University of St Andrews.

Julien Laizé

Head of CTM External Manufacturing, Valneva

Julien is an executive with an extensive and international experience in Vaccines and Biologics industry. He holds a Doctorate of Pharmacy from the University of Bourgogne, France, a Master in Pharmaceutical Engineering/Quality from the University of Bourgogne, France and a Global executive MBA from IE business school, Spain (top ranked business school). He has a good understanding and a global view of both pharmaceutical business and technical strategy.

Rich Nelson

Senior Manager, Global Logistics, PCI Pharma Services

Rich is the Senior Manager of Global Logistics for PCI Clinical Services in Rockford, IL, USA. He has been part of the PCI team for 9 years and is responsible for maintaining the global courier and depot networks, as well as managing IRT integrations, and Import/Export activities. Rich has over 15 years of experience in the Clinical Services industry, and has a Bachelor's Degree in Criminal Justice from Monmouth University.

Alex Weaver

Director of Engineering & HSSE, PCI Pharma Services

Alex has over 10 years of experience in the medical device industry. As the Director of Engineering, Alex is responsible for managing process engineering, project engineering, and facilities teams at PCI's headquarters in Philadelphia, PA. Alex's expertise was instrumental in leading the installation teams in implementing serialization equipment on various lines at PCI. He received his Bachelor's in chemical engineering, his Master's of Manufacturing Management from Penn State and is also a Six Sigma Black Belt.

Richard Williams

Senior Vice President CMC, Crescendo Biologics

Richard has over 20 years' experience in the biopharmaceutical industry, in particular in CMC project management and development of monoclonal antibody-based products. Prior to joining Crescendo, Richard was VP CMC at Kymab Ltd, where he established their internal CMC development functions and managed a network of contract manufacturing organizations. Richard has also held senior positions at Crucell (Janssen vaccines), CAT/Medimmune, Acambis and Schering Plough Animal Health. Richard received his PhD from the University of Surrey, Guildford, UK.

Akriti Seth (Moderator)

Senior Reporter, Informa Pharma Intelligence

As a correspondent for Channel NewsAsia, Singapore and for India Technology News, Akriti has covered a wide range of subject-matter including politics, economics and technology for a B2B audience. She has also gained experience working for Bloomberg TV India and Mid-Day Mumbai. Akriti is a graduate of the University of Mumbai and holds a masters from Mumbai's Xavier Institute of Communications.