The Role of a CDMO in the Fill/Finish of Large-Molecule Injectables

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Since the passing of the Biologics Control Act in 1902, the large-molecule sector is emerging as the next generation of therapeutics in biopharma, at the forefront of drug development because of the potential for biologics to treat unmet medical needs. Their rise in popularity, and importance, can be witnessed by the growing number of biologics approvals: in 2020, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) approved 53 new molecular entities (NMEs), of which 13, or 25%, were biologics. New drug approvals from the FDA are also expected to generate significant value in 2021 with 10 drugs projected to reach potential blockbuster status by 2026, five of which are biologics, according to Evaluate Vantage.[1]

Biologics are typically derived from living cells, they are complex, and typically classified as proteins. Often given through injection, or infusion, these molecules transport drug to specific locations within the body before releasing the compound. Of course, today, the world is paying especially close attention to vaccines. Both the Pfizer and Moderna SARS-COV-2 vaccines are mRNA-based, which takes advantage of normal biological processes to express proteins and create a desired therapeutic effect while the Johnson & Johnson vaccine is based on adenovirus, which, when modified, enters cells but cannot make new virus particles.

Despite the laser focus on COVID-19 vaccines – both first and second generation – biopharma has not let other vaccine programs be derailed. But, to get these projects over the finish line, they find themselves in need of aseptic manufacturing (fill/finish) capacity.

The Last Mile of Vaccine Manufacturing

While biologics present their own formulation and development challenges, vaccines can be even more complex in terms of antigen composition and other components, such as adjuvants, which must be characterized and compatible to ensure final stability of the formulation. The final downstream – and some would argue the most critical – step in the manufacturing of large-molecule parenterals

consists of fill/finish, where the vaccines are filled in vials or prefilled syringes and packaged for distribution.

Some challenges faced during large-molecule fill/finish manufacturing include:

- **Maintaining product stability.** Biologics can be unstable, vulnerable to protein aggregation, and are sensitive to temperature and light.
- **Conducting effective inspections.** Biologics vary in appearance and viscosity and are packaged in containers that differ in transparency, color and thickness, making visual inspection for microbial contaminants challenging.
- **Filling.** Every biologic should be precisely filled to present the appropriate dose to the patient.
- **Complying with regulatory guidelines.** The finish and packaging stages include preparing the vial, stoppers, and other container closure components and arrangements for filling, sealing, validating, cleaning, and sterilizing. These critical steps follow specific guidelines outlined by regulatory authorities. For example, FDA's Center for Biologics Evaluation and Research (CBER) ensures that FDA's rigorous scientific and regulatory processes are followed by those who pursue the development of vaccines.

Because fill/finish is a critical part of the biopharmaceutical manufacturing process, even the smallest mistake can lead to production failure which equates to an overall loss with an already expensive product. And the specialized aspect of fill/finish can impact the rate at which product reaches clinical trials or the market.

Biologics CDMOs Are Equipped for Aseptic Fill/Finish

To address these challenges, special processes, procedures, and complex mechanical equipment (filling, dispensing, and sealing systems) must be in place to ensure product integrity during fill/finish manufacturing. This often leads biopharma companies to partner with a contract development and manufacturing organization (CDMO) that has the knowledge, experience, and equipment to handle large-volume injectable fill/finish development and manufacturing. Fill/Finish providers can offer specialized services in such areas as the types of primary packaging containers used (ampoules, cartridges, syringes and vials), types of biologics, and scale of operation (preclinical, clinical and commercial).

Biologic CDMOs play a critical role in this market and have invested in new facilities and technologies to cater to a wide range of clients. As a result, it is no surprise that the global biologics CDMO market, valued at $9.93 billion in 2020, is expected to reach $18.90 billion by 2026.[2]

Aseptic fill/finish by a CDMO is the step-by-step method of making a formulation, filling it into primary packaging and then finishing by inspection, labeling, and packaging — all while keeping it contaminant free.

The aseptic process typically includes:

1. **Drug Sterilization:** The biologic must be sterilized before the filling process begins, typically accomplished via filtration.

2. **Component Sterilization:** All equipment, components, and containers are sterilized with steam autoclaves, dry heat tunnels, fumigation, radiation technology, and e-beams.

3. **Aseptic Filling:** Sterilized containers are transferred to filling machines, filled with sterilized drug, and then stoppered and sealed with a closure system.

The goal throughout the process is to make safe, effective products that are free of microbial or other contaminants.

The Primary on Packaging

A CDMO can help you choose the type packaging for the aseptic fill/finish of your large molecule biologic: primary (i.e., vials or prefilled syringes) and secondary (i.e., cartons and labels on vials).

For the purpose of this discussion, we are focused on primary packaging.

Choosing the correct container for a biologic injectable is crucial for the stability of the drug and the safety of the patient.

Packaging material for vials and prefilled syringes used during the aseptic manufacturing process typically includes:

- Borosilicate glass has excellent barrier properties, chemical resistance, regulatory acceptance, and a broad range of applications served.

- Polymeric materials such as cyclic olefin copolymer (COC). This combines glass and COC for greater formability, break resistance, lightweight, glass-like

transparency, strong barrier, and chemical compatibility. These systems are ideal for high-value, complex molecules.
    - One example is the Crystal Zenith® CZ system from West Pharmaceuticals. CZ addresses the need for a clear, biocompatible material that overcomes problems inherent in glass vials, syringes, and cartridges. Drug containment and delivery systems manufactured from the CZ polymer are ideal for high-value molecules, biologicals and biopharmaceuticals, where glass may be a less desirable option because of issues such as chemical interactions and breakage

- A hybrid material consisting of a molded, engineered polymer and an inert glass-like barrier coating system, such as the SiO2 system. The inert glass-like barrier is chemically resistant, contaminant-free, and consistent surface irrespective of the container geometry or materials of construction.

As the biopharma industry seeks to bring large-molecule injectables to market, many see the value of partnering with a CDMO to handle the last, and critically important, fill/finish of their product. A biologics CDMO will have the equipment and know-how to overcome the complexity of aseptic manufacturing and still get product to clinical trials and the commercial market on time.

References

1. Tracking Biologics: What's in Store for 2021? Patricia Van Arnum*, DCAT,* February 3, 2021.
2. Biologics Contract Development and Manufacturing Organization (CDMO) Market - Growth, Trends, COVID-19 Impact, and Forecasts (2021 - 2026), ResearchandMarkets, July 2021.

About the author
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Devan has held roles of increasing responsibility in Project Management leading key development and commercial programs for Pii for both the orals and injectables. With his leadership, Pii has built a world-class Project Management Organization (PMO) consistently characterized by a superb customer experience. Over the years, Devan has used his knowledge and technical skills to play a vital role for the Operations team, managing key initiatives for the Parenteral/Sterile business unit, including managing the overall scheduling and planning of all Aseptic Operations. His collaborative style when working with cross-functional teams across Pii's business units and ability to anticipate problems before they occur as raised the role of project management to an art form. Devan delivers a positive, outcomes-focused experience for our client-partners, from initial contact through successful completion of each project.
Devan earned his Bachelor Degree in Cell Biology and Molecular Genetics from the University of Maryland and an M.B.A. from Johns Hopkins University.

About Pii

Pharmaceutics International, Inc. (Pii) is a contract development and manufacturing organization (CDMO) with a passion for solving problems efficiently with the highest quality standards. Pii's Analytical Research & Development scientists pride themselves on their experience and ability to expedite method development and tech transfer in support of complex sterile fill/finish projects.
Pii's Hunt Valley, Maryland campus includes 70 manufacturing suites with 4 integrated aseptic filling lines delivering quality, safety, and efficiency. Our professionals have extensive experience with small and large molecule compounds, developing and manufacturing complex parenteral drugs, extended-release formulations, non-aqueous injectable drug products, and lyophilization. Learn more at https://www.pharm-int.com/.