WHITEPAPER

How to **mitigate risk for biologics** during fill/finish manufacturing

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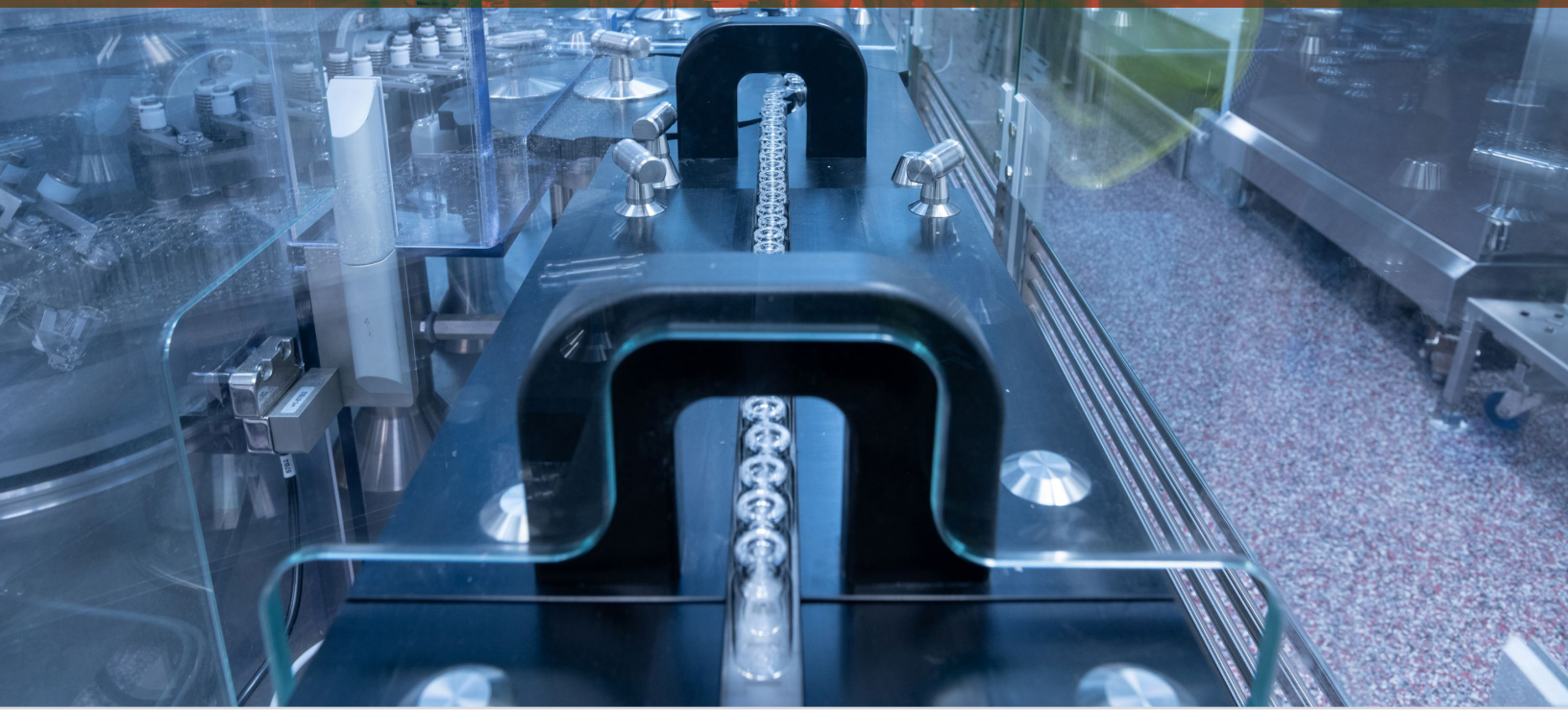
How to **mitigate risk for biologics** during fill/finish manufacturing



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Fill and finish are the last steps in the manufacturing process before biologics are packaged and labeled for shipment and administered to patients. Aseptic filling processes assure these high-value therapies—as well as the equipment and containers they touch—are sterile and free from contamination.

To move complex biologics successfully through manufacturing to clinical trials or commercial release requires more than state-of-the-art equipment; it requires specialized expertise, streamlined workflows and facilities with integrated, comprehensive capabili-ties and current good manufacturing practices (cGMP) experience. Contract development and manufacturing organizations (CDMOs) that provide all of these aspects offer the highest chance of pro-viding clients fill/finish biologics manufacturing solutions with the greatest degree of accuracy and the least risk of contamination.

CDMOs implement rigorous quality and risk control measures to prevent exposure to harmful microorganisms and/or other poten-tial sources of contamination. However, contamination remains of great concern for both manufacturers and the biopharmaceutical companies they serve. Inaccurate dosing to the vial is another risk, especially for small-batch products.

As more protein therapeutics, cell and gene therapies, and other large molecule drug substances move through the research and development pipeline, so does the demand for aseptic fill/finish services. With increased production comes greater need for asep-tic processing with the highest degree of sterility assurance, filling accuracy and quality. Anything less impacts regulatory compliance, project timelines and—most importantly—patient safety.

Products developed from living systems and injected into the body are naturally subject to a high degree of regulatory scrutiny. So too are the facilities that manufacture these products. Biologics manufacturers must follow cGMP regulations under 21 CFR parts 210 and 211, as well as applicable regulations for biologics under 21 CFR parts 610 through 680.[1]

This white paper provides information to help biologics developers make more informed decisions around selecting the right fill/finish manufacturing partner. It discusses the benefits of advanced tech-nology, integrated services and biologics expertise. When pharma-ceutical and biotech companies partner with CDMOs that embody these pillars, they raise their potential to deliver products to patients efficiently while maintaining the highest sterility assurance.

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From fixed to flexible: The move to closed-barrier, automated processing

Due to their favorable safety profiles, low generic competition and ability to deliver highly effective, targeted treatment, development of biologics and biosimilars has grown steadily over the past several years.

According to the American Society of Gene and Cell Therapy, as of mid 2022, 19 gene therapies, 18 RNA therapies, and 59 cell therapies have been approved for clinical use globally, with thousands of products in clinical trials.[2] The Alliance for Regenerative Medicine reports there are now 1,369 cell and gene therapy developers worldwide, up 5% from 2021.[3]

Additional activity in biologics and biosimilars has put greater demand on fill/finish manufacturing, and the move toward isolator technology has become increasingly popular. Choosing a CDMO that has the advanced equipment and technical expertise to manage these projects in a streamlined fashion is critical.

Complex formulations produced in small batches have characteristics distinct from small molecule drugs. A few of them include:

- Susceptibility to oxidation
- Degradation from shearing by mechanical actions such as impeller-based mixing
- Light sensitivity
- Molecular instability especially at high concentrations

Specific fill/finish capabilities are required to accommodate these characteristics. Because of biologics' fragility as well as strict sterility requirements, fill/finish operations necessitate a timely, quality-first approach[4]

"As an industry, there's been a push to understand and challenge the perceived risks of a conventional filling line," said Daniel Perrin, Director of Manufacturing for Emergent Biosolutions, a global CDMO with manufacturing facilities in the United States and Canada. "Emergent responded by examining guidance provided by the FDA, Health Canada, the Parenteral Drug Association, and other industry leaders. We took that information in stride and strategically invested in state-of-the-art isolator technology to offer our clients the highest sterility assurance we could provide."

To optimize speed to market, flexibility and scalability, as well as to reduce the risk of contamination, many CDMOs have moved from stainless steel equipment to single-use systems. In line with this trend, companies are also moving away from restricted access barrier systems (RABS) to closed-barrier aseptic isolators. Gloveless isolators with robotic handling provide another layer of assurance by completely removing personnel from the filling environment.

Removing the human element

While conventional lines and fixed RABS are suitable for biologics production, isolator technology offers many advantages for manufacturing large complex products. With conventional lines, container changeover, cleaning, sterilization and validation processes all add hours to days to processing times. They also require operators, which, even with all precautions taken, introduce risk.

"Human operators are the highest source of contamination," said Daniel Perrin, Director of Manufacturing. "That potential for contamination introduces product and patient safety risk. With newer technology available, regulatory agencies now expect manufacturers to use technology such as isolators."

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Director of Manufacturing for Emergent Biosolutions.

Closed-barrier aseptic isolators with single-use filling systems and gloveless robotic handling provide more suitable environments for biologics. Advantages of these systems include the following:

- **Control over aseptic filling**. Prefilled syringes allow physicians to administer medication quickly with less room for error. In manufacturing, these products risk air bubbling and needle drips. The Cytiva SA25, a gloveless robotic isolator, performs filling and closing mechanically, which reduces or eliminates air bubbles and leakage. Accuracy ensures patients will receive the correct dose when a product is being administered.
- **Sterility assurance**. With robotic operation and no glove ports, risk of human-borne contamination is essentially eliminated. "We can run our aseptic operation on a conventional line, and study and validate that process to minimize the risk to the product and to the patient," said Perrin. "As the industry has matured and regulatory expectations have changed, we don't want to rely solely on testing, however. We want to follow quality-by-design to engineer the risk out of our processes. We want our customers to have the assurance that the probability of an occurrence is so low that every vial coming off that line is sterile."

A study evaluating usage data from eight companies using the Cytiva SA25 from 2018 to 2021 found no cases of microbial growth in more than 250 media fills.[5] "On a closed system with a robotic isolator, there is no opportunity for contamination, because it's designed in such a way that you cannot intervene," said Perrin. "There are no glove ports. If you need to fix or change something, you use the robot. Since implementing our machine, our risk to product contamination is almost nonexistent."

- **Eliminates glass-to-glass contact**. The presence of glass particulates in drug product or substance is a common reason for recalls.[6] Traditional fill lines use star wheels and similar components, which introduce risk by promoting glass-to-glass contact. Closed-barrier aseptic isolators are designed with sterile, nested vials that don't introduce contact. "By removing glass-to-glass contact, glass particulates aren't generated, which increases batch yield by reducing the number of units rejected during product inspection," said Perrin.
- **Maintained product quality**. Bio-decontamination by design positively affects product quality. Replacing manual processes with automation improves consistency, which also affects quality. A study evaluating CAR-T cell fill/finish manufacturing concluded a closed workflow reduced cell exposure to dimethyl sulfoxide DMSO before freezing compared to open processes.[7]
- **Flexibility**. The aseptic process was designed for flexibility and sterility assurance. Fixed systems with an open flow path require time-consuming assembly, cleaning and sterilization, disassembly and material storage. Processes also require validated clean-in-place (CIP) and/or steam-in-place (SIP) protocols.

Single-use assemblies don't need cleaning and sterilization, eliminating potential failure modes from the process. Removing operational complexity allows manufacturers to move from fill to release faster than with conventional systems. It also allows for greater flexibility in the filling line.

"Everything that touches the product is single use," said Perrin. "We have an efficient standard process that allows us to easily bring in new components for a project."

The benefits of automation and standardization

Automation has become a core feature of current fill/finish equipment. It reduces risk of contamination introduced by human interaction, particularly when loading raw materials, performing system changeovers, and cleaning.[8]

Automation also standardizes processes subject to variability. Standardization improves efficiency because machines perform repeatable tasks consistently without fatigue or error. It also frees up operators' time for higher-value tasks. All these factors allow CDMOs to produce more batches daily than they would using manual processes.

Automation, especially when combined with single-use systems, streamlines tech transfer. With approaches and equipment standardized, moving to the next phase of production becomes more efficient.

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Scaling up: Best practices for biologics fill/finish

Manufacturing scale-up is usually part of a larger tech transfer project. The end goal is to prepare for clinical or commercial production. Maintaining yield during production and resolving impurities are common challenges during scale-up. But what happens when there's not enough product to lose?

Technology designed for small batches, combined with personnel with experience processing small-batch biologics, mitigates expensive volume loss and contamination. "A biotech company may only have half a liter of product. A compliant, gloveless, robotic machine fills that niche incredibly well," said Perrin. "We have filled batches that were between 50 and 70 vials. That was nearly impossible a few years ago, and we're doing it successfully today."

Biologics developers must also consider the risk involved in multiple tech transfers. Partnering with a CDMO with end-to-end service offerings will help lower the odds of variability during a process redesign. Keeping most manufacturing services under one roof also improves efficiency (and, relatedly, speed) due to improved communication.

"With an end-to-end service provider like Emergent, you're working with largely the same team," said Perrin. "We have drug substance platforms and complex formulation experience. We understand exactly what clients want to accomplish to overcome their challenges. Complete visibility and ownership can reduce risk and be more cost effective."

Emergent's clients are assigned a project team that includes both quality assurance and operations experts, which ensures quality is built into the plan from day one. A dedicated project manager then guides the project from development and cGMP production through to commercial release.

The next phase: Getting products to patients

Because speed to market and cost are primary considerations when developing and commercializing biologics, shaving months off fill/finish manufacturing time is a significant advantage. Partnering with an integrated CDMO service provider streamlines processes to help bring products to patients faster.

The Cytiva SA25 offers two-hour batch-to-batch turnaround, with as little as 50 to over 80,000 vials per batch. Rapid tech transfer means new products can be integrated and filled within weeks.

mRNA Project Completed in One Month

A client who was new to Emergent was in desperate need of mRNA material to support a time-sensitive clinical trial. The client had a limited quantity of product (0.5 L) and required a minimum of 50 vials delivered.

Following initial conversations with SMEs at Emergent, the project moved forward. Emergent understood the criticality of batch yield and focused on minimizing line losses during the operation. The fill was completed within one month of the project kick-off meeting. The customer received their product on time, totaling 74 vials.

Working with an experienced and specialized team also enables faster execution. "We understand the critical steps during any stage prior to fill," said Perrin. "During late formulation we know what to anticipate during inspection. We also have over six years of experience with gloveless robotics, so we can hit the ground running."

Conclusion

When it comes to biologics development and production, the smaller the batch, the higher the value per dose. To maintain the highest integrity for every molecule, and to get them from the plant to the patient safely, fill/finish manufacturing requires specific equipment, facilities and expertise.

A closed-barrier aseptic isolator with single-use filling systems and gloveless robotic handling best protects high-value biologics from contamination. When it's offered in tandem with integrated service offerings from a CDMO with significant biologics expertise, biopharma companies can benefit from efficiency gains, compliance and the assurance that the product administered to patients meets the highest quality standards.

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Emergent has the scientific and regulatory experience, end-to-end development and manufacturing resources, and efficient technology transfer capabilities that can harness the urgency, acuity and scalability to bring life-saving, life-extending products to market.