ReciBio Pharm

Overcoming the complexities of ATMP fill & finish

EXECUTIVE SUMMARY

As our understanding of molecular biology and genetics progresses, biologics in development are providing previously unattainable therapeutic benefits. However, the emergence of innovative advanced therapy medicinal products (ATMPs) brings new development and manufacturing complexities.

In this white paper, our experts Cambria Monroe, Associate Director, Manufacturing and Brad Londot, Senior Director, Facilities and Engineering at ReciBioPharm explore the challenges ATMPs are bringing to a critical stage of production: fill & finish. They outline the strategies needed to navigate these hurdles and highlight the benefits a contract development and manufacturing organisation (CDMO) with ATMP experience and expertise can offer in ensuring cutting-edge new therapies reach patients.

The rising potential of biologics

Over the last 30 years, the potential of biologics has expanded as a result of technological advancements and our growing understanding of molecular biology and genetics. The development pipeline is now seeing increasingly advanced biologic therapies that offer hope for patients suffering from previously untreatable diseases. These novel modalities include:

RNA-based therapeutics and vaccines

The potential of RNA-based therapeutics was highlighted throughout the COVID-19 pandemic, when mRNA technologies offered inexpensive, scalable and fast production, enabling the rapid global rollout of vaccines. In the wake of the pandemic, RNA-based therapies are being developed to treat and protect against a wide range of conditions including rare diseases, cancers and infectious diseases[1,2].

Oncolytic viruses (OVs)

Due to their ability to enhance anti-tumour immunity and selectively attack and kill cancer cells, OVs have gained increasing attention in the biopharma industry as part of combination therapy for various cancer types[3]. The potential of oncolytic adenoviruses has recently been highlighted following clinical trial success in bladder cancer patients who were unresponsive to mainline treatment[4].

Viral vector vaccines

Through genetic engineering, viral vectors can introduce genes encoding key antigens of pathogens to patient cells, helping to train the immune system to recognise the corresponding virus or viral protein component. Viral vector vaccines have been developed to protect against many infectious viruses, including Zika, HIV, malaria and Ebola[5].

Gene therapies

Viral vectors are also proving to be efficient and effective tools to deliver genetic material to patients, replacing missing or abnormal, disease-causing genes with a functioning version.

There are now 27 gene therapies approved for use globally, targeting indications including rare diseases, various cancers and neurological disorders[6]

As they often offer significant therapeutic benefits over chemically produced small molecule drugs in treating severe illness, it is no surprise that biologics are predicted to overtake small molecules in terms of sales revenue by 2027[7]. The global biologics market is consequently anticipated to grow from $348.03 billion in 2022 to $620.31 billion by 2032[8].

The emergence of ATMPs — including gene therapies, as well as certain viral vector vaccines and RNA-based therapies — represents a significant growth driver in the biologics market. Between 2022 and 2030, the ATMP market alone is expected to grow at a compound annual growth rate of 16.8%[9].

Meeting these predictions and ensuring revolutionary new ATMPs are delivered to the patients who need them relies on the success of a critical manufacturing step: fill & finish.

MEETING THE FILL & FINISH NEEDS OF THE GROWING BIOLOGICS MARKET

Due to their delicate nature, most biologics must be delivered to patients via injection or intravenous (IV) infusion. These forms of administration allow the biologic to avoid the harsh conditions of the gastrointestinal (GI) tract and first-pass metabolism. However, direct delivery into the bloodstream also means the biologic will bypass many of the body's first lines of defence against harmful agents.

As an integral step in manufacturing, sterile fill & finish ensures the safety and quality of biologics before their introduction to patients. The fill & finish process will typically involve sterilising and combining the drug product, container and container closure system. Visual inspection is also a critical aspect of the fill & finish process, particularly for sterile injectable products, to ensure the absence of visible defects, contaminants, particles, or container damage. Developers and manufacturers must carefully consider how decisions made throughout these processes could impact the drug's stability (and therefore potency), accurate dosing and safety. This is not only critical to ensuring patients receive safe and effective therapeutics but also to meeting regulatory requirements.

The biologics fill & finish process is complex and highly specialised, requiring significant expertise and resources. It also often necessitates purpose-built facilities, equipment and processes, particularly to meet the intricate needs of ATMPs. As a result, biopharma companies are increasingly looking to expert contract development and manufacturing organisations (CDMOs) to support their biologics fill & finish projects and help them overcome the many challenges that can arise.

BIOSAFETY LEVELS FOR ATMP FILL & FINISH

To ensure the safety of both patients and manufacturing personnel, biologics fill & finish must be conducted in settings that meet the appropriate biological safety level (BSL). The Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control specify the biosafety levels required for biological agents in the US and EU, respectively.

There are four biosafety levels (BSL-1–4), with BSL-1 being the lowest and BSL-4 the highest. As the manufacturing of many ATMPs requires the handling and manipulation of pathogenic or infectious organisms — including viruses such as adeno-associated viral (AAV) vectors, adenoviral vectors and lentiviral vectors — BSL-2 labs are required.

As well as BSL-1 safety protocols, covering the use of personal protective equipment (PPE), biohazard signs and daily decontamination of work surfaces, BSL-2 safety protocols include:

- Conducting all procedures that could cause infection from aerosols or splashes within a biological safety cabinet
- Decontaminating infectious materials before disposal (typically using an autoclave)
- Using additional PPE when needed, such as face shields.

EXPLORING THE CHALLENGES OF BIOLOGICS FILL & FINISH

The biologics fill & finish process is often associated with complexities. As innovative drug modalities such as ATMPs enter the development pipeline, developers and manufacturers are facing further fill & finish challenges that require creative solutions to overcome.

1 Meeting the unique needs of different projects

Biologics come in many different forms, from small recombinant proteins to large multi-component viral vectors with a protein capsid and/or envelope and a genetic payload. As biologics encompass a diverse range of molecules, each will have distinct needs that must be met to ensure patients receive a safe and efficacious therapy.

How does fill & finish differ between small molecules and biologics?

Although biologics fill & finish processes can be similar to those of small molecules, these large and highly complex molecules are often labile, which adds complexity.

Compared with small molecules, the stability of biologics is more likely to be impacted by the conditions applied throughout fill & finish, leading to aggregation or changes in conformation. These conditions can include:

- High temperatures
- Varying pH
- Mechanical agitation
- Freeze-thaw cycles.

Additionally, biologics can become viscous at high concentrations, potentially causing issues with dosage accuracy. As some biologics are also prone to surface adsorption, developers and manufacturers must also consider how their choice of primary packaging could lead to product loss. This is a common issue with some viral vectors, which can show non-specific adsorption to solid surfaces including glass, plastics and stainless steel surfaces[10,11].

Although many biologics — particularly ATMPs — will rely on BSL-2 containment in filling lines, the equipment used, vial sizes and formats, and strategies to maintain stability can differ substantially based on the project's characteristics. Key project needs that could impact the decisions made in biologics fill & finish include:

Considering patient population needs

The fill & finish needs of a project will be closely linked to the target indication. Therapies developed aiming to treat a large patient population, such as vaccines, will inherently require the fill & finish of larger volumes of drug substance than therapies designed to target small patient populations, like gene therapies.

Biologics developers and manufacturers must therefore consider whether the equipment used in fill & finish can support the required batch size, fill volumes and vial size formats, as these can vary greatly (as demonstrated in Table 1).

Equipment					
		VarioSys Skan Isolator, Bausch+Ströbel Filler	Vanrx Cytiva Isolator and Filler	BOSCH AFR 1020 RABS SYSTEM	Automatic dispenser
Key parameters	Automation	Semi-automated	Fully automated	Fully automated and manual	Manual filling
	Formats	Glass and Crystal Zenith® vials	Glass vials, syringes or cassettes	Fully automated: Glass vials Manual: Glass vials and cryo-vials	Glass vials
	Fill volumes	0.25 mL and greater	0.5 mL to 100 mL	Fully automated: 0.5 – 1.6 mL Manual: Up to 4.5 mL Cryo-vials: 0.2 – 1.0 mL	0.5 mL to 2 mL
	Batch size (supported by Media Fills)	100–15,000 vials/ batch	2R – 5,000 vials 10R – 3,000 vials	30,000 vials (automated line) 1,500 vials (manual)	Up to 1,500 vials/batch

Table 1. The differences between the key parameters of four different filling lines available at ReciBioPharm.

Selecting container formats

The chosen container for a biologic will depend on the dosage and the formulation. Typical containers for biologics are made of glass or plastic, including vials, cartridges and pre-filled syringes. In liquid formulation, biologics with a higher dosage will inherently require vessels that can support larger volumes.

Key considerations in format selection include ensuring the formulation is compatible with the container and closure material used and understanding the biomolecule's sensitivity to the proposed storage conditions. The container must also be carefully selected with consideration to the final storage conditions and volume of the product. This is particularly important when liquid sterile injectables are frozen in storage, which will result in expansion and potential container damage if it is not large enough.

Ensuring the stability of the biologic is maintained throughout storage and transport on the journey to patients relies on minimising the potential for extractable/leachable, oxidation, pH changes and adsorption.

Ensuring stability

As well as considering how container formats could interact with the formulation, biologics developers must also determine how else stability could be affected throughout fill & finish.

As lyophilisation can extend the stability of their biologic by slowing drug product degradation through the removal of moisture, developers often choose to rely on this method over liquid formulations. However, lyophilisation can add complexity to fill & finish, with the need for scalable, reproducible processes that can be precisely controlled.

Maintaining product stability also relies on the incorporation of controls to protect temperature-sensitive products, like mRNA therapeutics. This could include investing in cold storage options and developing processes that ensure speed as the product moves between filling and cold storage.

Additionally, visual inspection plays a crucial role in safeguarding the stability of a biologic throughout the fill & finish process. As part of quality control (QC), visual inspection will involve the assessment of container integrity, storage conditions, the number of containers and more. Manual visual inspection is standard in both the US and EU, requiring highly skilled operators.

2 ATMPs are adding complexity

Another challenge facing biopharma developers and manufacturers is meeting the unique needs of the many ATMPs entering the development pipeline.

Gene therapies in particular are expanding complexities in fill & finish. As they are highly personalised, gene therapies are generally only used to treat small patient populations. Although gene therapies can potentially provide a long-term treatment benefit with a single dose to these patients, their high production costs could result in limited patient access. The gene therapy Hemgenix, a one-time gene therapy treatment for haemophilia B, currently takes the position of "most expensive therapy in the world," priced at $3.5 million[12].

The high cost of gene therapies means any material lost through the fill & finish process could cost millions and ultimately limit the number of patients who could be treated. However, not all fill & finish machinery is built to minimise loss, particularly line loss (with drug product left in the tubing). For ATMPs, it is therefore critical that developers and manufacturers rely on equipment specifically designed to deliver accuracy and prevent loss where possible.

3 Ensuring compliance with stringent regulatory guidelines

To safeguard quality and safety, biologics producers must comply with rigorous guidelines throughout fill & finish, as mandated by regulatory bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Developers and manufacturers must consider the control measures and equipment that will be used to achieve sterility and meet these stringent requirements.

As active biopharmaceutical ingredients are typically sensitive in nature, terminal sterilisation and irradiation are often not an option to ensure sterility, meaning many biologics cannot be sterilised in the final container. As a result, biologics generally require aseptic processing — where the container and closure are sterilised separately before the addition of an aseptically formulated product. This must be carried out in a strictly controlled environment.

Regulators encourage the use of restricted access barrier systems (RABS) or isolator technologies in aseptic processing to minimise direct human intervention and reduce the risk of microbial ingress. Retrofitting these technologies is not always a viable option. For less stringent steps of sterile product manufacturing, Grade C cleanroom backgrounds will also be needed.

Overcoming fill & finish challenges with an expert CDMO partner

Meeting the needs of biologics throughout fill & finish is only becoming more complex as revolutionary ATMPs enter the development pipeline, bringing new challenges. By relying on a CDMO partner offering the right capabilities, expertise and flexibility needed to overcome these hurdles, biologics developers can ensure the reliable delivery of critical therapies to the patients who need them.

Capabilities and capacity

To effectively meet the fill & finish needs of biologics, developers must have access to suitable capabilities. Installing the necessary technologies, equipment and facilities to support biologics fill & finish, as well as the carefully designed cleanroom spaces, requires significant investment. By identifying an expert CDMO that can offer the necessary capabilities to achieve quality and precision, biologics developers can avoid the significant investment needed for in-house fill & finish.

Equipment supporting ATMP projects

It is important that ATMP developers determine whether the CDMO has the appropriate equipment and technologies to support the project, including systems like the VarioSys Skan Isolator, Bausch+Ströbel, which enables:

- Extremely low line loss (<10 mL in filling assembly)
- Flexibility in vial formats
- Low fill volumes (as low as 0.25 mL)
- Small batch sizes (as low as 100 vials)
- Single-use flow paths to minimise cross-contamination.

It is not only critical that the chosen CDMO has the appropriate equipment, technology and facilities to support the project's needs; it must also have capacity. Wait times to start filling projects have reportedly increased up to 12–18 months, with many manufacturers struggling to meet fill & finish demand[13]. With any time lost waiting for fill & finish to commence representing longer time frames to patients, it is vital to identify a CDMO partner with capacity and imminent availability to prevent delays.

Committed experts
Representing an integral stage in ensuring the safety and quality of a biologic, fill & finish must be supported by experts who understand what it takes to meet regulatory requirements and optimise the processes involved.

Progressing biologics from early clinical phases to commercialisation relies on passing critical regulatory milestones, providing data and information to support applications at each stage and demonstrating compliance with stringent guidelines. CDMOs with a track record of regulatory excellence and a strong established relationship with regulatory bodies will be able to guide developers as their project progresses while ensuring all the requirements for fill & finish are met.

Leveraging a global network of experts in fill & finish, CDMOs can optimise processes to meet the unique needs of each project while ensuring compliance, safety and quality. Applying the lessons learned from years of fill & finish experience, expert CDMOs can also identify potential risks and apply creative solutions to avoid delays, helping therapies reach the patients who need them quicker.

Flexibility to support changing needs
As biologics become more complex, it will be increasingly important for CDMOs to demonstrate flexibility, particularly as these projects progress and scale up to commercialisation. CDMOs demonstrating flexibility will:

- **Support from early clinical phases to commercialisation**
  Relying on a CDMO that can support biologics projects from early clinical phases to commercialisation can help to ensure that the changing fill & finish needs (such as batch size) are met as the project progresses. These companies will offer a comprehensive range of line configurations and vial formats. It is important to remember that not all CDMOs offer commercial-grade capabilities and time could be lost if a new partner must be found.
- **Offer integrated capabilities**
  By providing integrated capabilities to support ATMP production from plasmid manufacturing to fill & finish, CDMOs can speed up tech transfer and prevent issues through collaborative communication between teams on the same site.
- **Provide the potential to expand**
  As projects progress, it can also be advantageous to partner with a CDMO that can expand in the future and incorporate new technologies, working with developers to meet growing fill & finish demand and adapt to changes in requirements.
- **Have a network of clinical and commercial-ready sites**
  CDMOs with multiple locations in the US and EU to provide support can further enable flexibility, allowing developers to conduct filling near clinical sites or in proximity to their own site if needed.

LOOKING TO THE FUTURE OF FILL & FINISH

As we look to the horizon, the biopharma industry can anticipate growing numbers of innovative biologics — particularly ATMPs — to emerge, providing new treatment options and helping to improve patients' lives.

However, these revolutionary yet complex new drug modalities will continue to bring new challenges in fill & finish, from supporting small-batch manufacturing to ensuring product stability.

With rising demand for these novel therapies, developers will need to increasingly look to CDMOs offering the necessary capabilities, expertise and flexibility for manufacturing support, including fill & finish.

PARTNERING WITH RECIBIOPHARM

We're dedicated to supporting you and your biologic at every stage of your journey from our network of clinical and commercial-ready sites across the EU and US. Our global infrastructure provides the enduring platform required for a nimble, proactive and consultative approach to every project, helping you overcome the challenges of ATMP production.

Offering a wide range of sterile fill & finish capabilities, we can support your biologic as it progresses from early clinical phases to commercialisation. Leveraging equipment developed to provide minimal line loss and high fill accuracy, we support your high-quality small-batch ATMP production.

Discover how we can support your next ATMP fill & finish project >>

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About us

ReciBioPharm, Recipharm's biologics business combining the capabilities of acquired CDMOs Arranta Bio, GenIbet and Vibalogics. Our expanded biologics drug development and manufacturing services encompass technologies based on live viruses and viral vectors, live-microbial biopharmaceutical products, recombinant proteins, nucleic acid-based mRNA and plasmid DNA production.

Established in 1995, Recipharm's manufacturing, fill & finish, and delivery-device services encompass a wide variety of drug dosage forms and modalities. Recipharm is an industry leading CDMO with over 25 facilities and 6,000 employees globally – supporting companies that are developing small molecules and biologics. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden and the US.