Meeting Growing Demand: Fill-finish and Cold Chain Strategies and Tactics

The demand for contract development and manufacturing organisations (CDMOs) offering fill-finish and cold chain logistics services is on the rise. Driven by the COVID-19 pandemic, there is increasing need for external partners to produce and distribute treatments and vaccines. CDMOs also face the challenge of adapting to the development and manufacture of new and more complex biologics, such as cell and gene therapies (C&GTs) and mRNA technologies.

Prospective CDMO partners will need to offer not only significant dedicated capacity but specific expertise to successfully deliver contract fill-finish and cold chain services to meet market demands. They will need to carefully consider the sorts of containers and storage types used, as well as understand how their cold chain capabilities can be validated. Throughout fill-finish, CDMOs will also require a thorough understanding of how sterility of the final product can be ensured.

In this article, David King, Head of Drug Product Operations at Samsung Biologics, discusses the challenges CDMOs face meeting the growing global demand for high-capacity fill-finish and cold chain capabilities. Explaining how careful organisation and effective communication can support more successful drug programs, David offers his perspective on the strategies and tactics it takes to deliver a better program and patient outcomes.

The Increasing Importance of Cold Chain Capabilities and Effective Fill-Finish Processes

The biologic drug product market has seen significant growth in the last decade. This trend is set to continue in the next few years, with the global market predicted to reach $421.8 billion by 2025, at a compound annual growth rate (CAGR) of 8.1% from 2020.[1]

The need for vaccines and advances in drug technologies, such as mRNA, throughout the COVID-19 pandemic has fuelled the recent explosive rise in biologic drug development and manufacturing volume. As a result, there has been increased demand for cold chain capabilities and fill-finish processes to support these projects.

The COVID-19 pandemic has also contributed to the need for accelerated product development to enable biologic drugs to enter Phase I and Phase II clinical trials sooner. Consequently, rather than spending considerable time in formulation development, manufacturers are opting to rely on cold storage to maintain product stability over time.

Strain mutations and regular booster vaccinations are likely to continue for the foreseeable future, meaning demand for fill-finish will persist. Additionally, future biotechnological advances will result in more COVID-19 related and non-related biologics on the market that rely on these capabilities.

Recognising the above, many CDMOs have already begun adapting by expanding their capacity and cold chain offerings to meet their clients' demands. However, manufacturers striving to adjust to these rising pressures must carefully consider the challenges they may face along the way and how they can be solved. By offering expertise, careful organisation, and effective communications, they will be well positioned to respond to the rising need for both cold chain and fill-finish capabilities.

Cold Chain Considerations: Offering a Range of Containers and Storage Types

The types of cold chain capabilities that biopharmaceutical companies require to manufacture biologics can vary greatly between projects. Therefore, there are many considerations and challenges that must be accounted for.

1) Container Selection

Deciding on the correct container for the biologic can be difficult, as there are many potential candidates: bags, bottles, vials, and cryovials. These can be made of various materials, such as different types of plastics or glass, so careful consideration will be needed as to the potential extractables and leachables expected for each type of container.

The decision also often relies on the product owner's platform. The chosen container must be easy to work with and also must be aligned with how CDMO partners operate. Manufacturers that can offer flexibility to their clients by being able to work with an array of potential containers will therefore have a distinct advantage over others.

2) Storage Capabilities

Although there are common ranges for freezing products, CDMOs must be able to handle multiple types of storage capabilities. The necessary standard operating procedures (SOPs) will also need to be in place for each.

For many biologic drug substances (DS), freezing rate is of great importance. This is particularly true for vaccines relying on live attenuated viruses, as the rate of freezing can impact their viability.

Blast freezers have traditionally been used in the freezing of bulk biopharmaceuticals. These freezers tend to have slow freezing rates, despite the name, and generally produce variable freezing rates throughout the bulk of liquid products. As a result, the product slowly freezes from the outside in. This can cause compression of the core volume by the slowly advancing solid frozen phase and can damage sensitive products within the bulk, such as complex proteins.

Control rate freezers, where the cooling rate can be increased or decreased at different points of freezing, can minimise potential damage to the product resulting from freezing. They

can also provide consistency in certain parameters, such as the degree of supercooling, between batches as compared with blast freezers. However, they are often more difficult to work with and require the manipulation of different containers and probes.

By offering a variety of storage capabilities, CDMOs will not have a single platform. This can be a further challenge, determining the most suitable conditions for storage for each individual project and optimising them throughout will take time.

3) Validation of Cold Chain Capabilities

Considerations need to be made to both static and dynamic handling validations of cold chain capabilities. Pharmacopeias globally provide guidance on cold chain storage and transport considerations. In particular, the U.S. Pharmacopeia (USP) <1079> Good Storage and Shipping Practices for Qualification describes procedures to maintain proper storage environments for products and to ensure a preparation's integrity until it reaches the user.

Static validations are associated with handling of the DS on-site, where there tend to be better temperature controls and less expected variation. Examples of static handling include large cold rooms (-40°C to 2–8°C) and small -80°C units.

Dynamic validations are associated with DS handling off-site, or as the product is being transported. The complexity of the dynamic validation is high because the control systems and expected temperature exposures are within a greater range. For example, the product is more likely to be impacted by seasonal temperatures during transport as compared with storage on-site. As a result, these systems are gaining more regulatory attention.

Throughout manufacturing, storage, and transportation of the biologic drug product, it is important to consider how the temperature and humidity controls will be monitored in real-time. CDMOs will also need to employ risk management systems and continuity plans in the event of temperature control failure.

Preliminary measures to avoid temperature deviation are also essential. These could include control centres ready to respond to alarms 24/7 and access to alternative suitable storage areas in the event of deviations that could impact the product quality.

Fill-Finish Capabilities: The Need for Sterility and Adapting to New Technologies

When considering fill-finish challenges, maintaining sterility is of the highest concern. CDMOs must strive to achieve a perfect, pure product with no contaminant particles or risk negatively impacting patient safety.

Sterile filtration for biologics is often the only means of sterilisation without destroying the product. Most of the time the process is conducted with two filters in-line with the flow of the product to the container closure (such as vials or syringes) during fill-finish. These sterilising filters are placed in grade A environments as close to the filling point (needles) as possible.

Filtration at this step is a critical part of the process and there are increasing expectations on companies to include a pre-use post sterilisation integrity test (PUPSIT) to detect any potential flaws in the filter. However, these in-place filter integrity tests require strong controls, as their performance has the potential to introduce contamination.

There must therefore be careful thought as to where potential contamination could come from. This includes raw materials, stoppers, and other equipment, meaning suppliers play a key role in reducing contamination risk.

The Challenges and Opportunities Created by New Technologies

With the COVID-19 pandemic highlighting the effectiveness and potential for mRNA technologies, more and more manufacturers strive to offer fill-finish capabilities to address its increasing popularity. However, mRNA technologies have also brought with them several new challenges.

Manufacturers that have previously predominantly worked with drugs that are water-soluble now work with unfamiliar mRNA products encapsulated with lipid nanoparticles. These technologies can be unpredictable and supporting these projects requires determination of the potential fill-finish conditions that could change the mRNA product characteristics.

Advances in technology have also come in the form of artificial intelligence (AI) and robots, which instead alleviate challenges, by minimising the potential of contamination throughout the fill-finish process. As humans provide the greatest risk of contamination, automated filling lines offer reduced risk. Visual inspection machines with AI capabilities can be further used to reduce human error and prevent contamination through manual procedures.

A Successful Project Needs More Than Just Capacity

It is not enough to be able to provide additional capacity for cold chain capabilities and fill-finish processes. The CDMO-sponsor relationship is critical too.

With a strong relationship and clear communication between the CDMO and biopharma company, a better understanding of the project and the potential challenges it may encounter can be built. Trust is key to sharing important information such as critical process parameters from the onset of the project. Having this information, as well as the right expertise available, will enable rapid understanding and optimisation of processes.

Taking ownership of the process also makes a big difference. CDMOs should be proactive in deciding how the product should be processed and launched, rather than acting passively. They must be disciplined and dedicated, ensuring that projects reach major milestones promptly on their way to commercialisation. This relies heavily on careful organisation by the CDMO to set and complete these milestones, including a date for the engineering batch and process performance

qualification runs. Not taking these milestones seriously could result in significant financial loss by the client, further highlighting the importance of working with a partner who takes ownership of the process.

CDMOs that embrace projects and truly care about the commercialisation and success of the project will always perform better than others.

A Look to the Future of Cold Chain Capabilities and Fill-Finish Processes

The reliance on CDMOs offering cold chain capabilities and fill-finish processes is likely to continue, especially considering that regular booster vaccines for COVID-19 will be expected in future. As with vaccines, demand to produce products at high volume will likely keep rising. Making processes for high volume projects more efficient (by aiming to produce a high yield with minimum product loss) can ensure product quality is maintained while output is increased.

A greater need for CDMOs that can manufacture new and previously unfamiliar products such as C&GTs, which require finesse and smaller scale production, can also be expected as advances in these technologies progress. Making processes more efficient and paying attention to yield factors is especially important for products like C&GTs where production costs are typically high.

It is therefore essential that biopharmaceutical companies choose their CDMO partners carefully and identify those that can predict and solve challenges that may arise surrounding cold chain capabilities and fill-finish processes.

REFERENCES

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David King holds a bachelor's in biology and has 29 years of experience in pharmaceutical and medical device industries. He was a microbiologist during first 5 years of his career at filter manufacturer Gelman Sciences and with a parenteral manufacture, Fuji-Sawa. He spent 7 years as a quality engineer with medical device manufacturers (Volcano and Tandem Diabetes) with a focus on sterilization (steam, gamma and ETO), leading the design/validation of a new sterilization process in-line with production. He has managed aseptic filling production facilities (Parke-Davis, Genentech, Jubilant HollisterStier, Samsung Biologics) for 18 years. He has extensive experience that include: complicated formulations, most container closure systems, tight project timelines, and leading manufacturing to profitability. David currently is the Director of Drug Product Operation at Samsung Biologics in South Korea, leading a team of 200+ employees in the introduction of biopharmaceuticals into established aseptic filling lines for both clinical and commercial markets.