Rapid Scale-Up of Cold-Chain Operations in Drug Development and Manufacturing

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INTRODUCTION

Reliable cold-chain supply, from active pharmaceutical ingredient (API) through to end product, often is misunderstood or treated as an afterthought: "freeze it and forget it." However, as more temperature-sensitive therapeutics are formulated and manufactured, manufacturers must prioritize frozen storage and cold-chain shipping as an individual unit operation. Like any other effective unit operation, cold-chain operations require thoughtful planning, risk assessment, and investment as well as accurate data collection.

In general, demand for cold-chain operations has been increasing for years, parallel with an increase in biological therapeutics that are temperature-sensitive, from vaccines to cell-and-gene therapies, Figure 1. While some organizations already have noted this trend and have begun planning cold-chain operations for future projects, others have been reactive to the process of scaling up their cold-chain. Regardless of where an organization starts, the same principles, the same considerations, and the same risks apply.

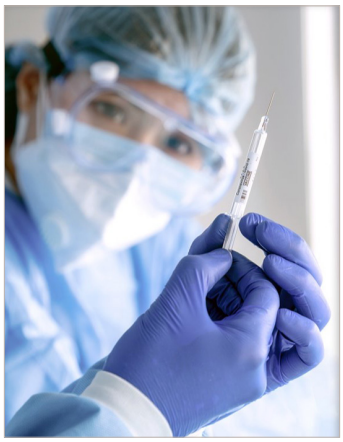

Figure 1. The rapid development of COVID-19 vaccines is an example of successful cold chain scale-up

DON'T GIVE PRODUCT INTEGRITY THE COLD SHOULDER

The "freeze it and forget it" perception originates, in some cases, from the stage of development. Typically, teams working at smaller scales – like a clinical stage or projects working through research and development – are not freezing large volumes of API. They likely are freezing in small vials or bottles. At that stage of development, prior to scale-up, freezing-and-forgetting is essentially acceptable; it is the entirety of the cold-chain process.

Understanding the cold-chain supply scale-up challenges that can threaten product integrity – during freeze/thaw, storage, and shipping – empowers manufacturers to implement efficient, cost-effective solutions.

However, when a project is ready to scale up, other parts of the process must be taken into consideration: bioreactors and chromatography columns need to get bigger, etc. Freezing also becomes more than just holding in place (i.e., "I just need a bigger freezer"). With scale-up comes increased stability risk across shipping and storage, as well as during the freeze/thaw cycling. Thus, cold-chain success – defined here as maintaining product integrity from pharmaceutical API to end user without damage or temperature deviations – depends on dedicating planning and resources to treat cold-chain as a unit operation of its own.

The first step for manufacturers is understanding their material: where it operates, where it is optimal. The biological product is the most vital component in the cold-chain. As scale-up begins, the manufacturer needs to understand the product's sensitivities, including maximum and minimum temperature ranges, pH level, UV light sensitivity, and sensitivity to different materials with which it may come into contact (i.e., whether it degrades faster or undergoes adsorption with certain materials).

Material awareness also comprises analyzing all product contact, aspects of where the biologic will be stored and transported, and weighing product sensitivities against all primary contact layers (often consumable components, such as single-use bags). The manufacturer also must understand the product's sensitivity to the freezing process and its planned distribution network (i.e., if the manufacturer is using contract manufacturers or utilizing their own facilities). In this undertaking, the manufacturer should have a roadmap of what volumes they would like to scale (e.g., their preferred sizes), both in the near term and looking ahead.

Step two for manufacturers prioritizing cold-chain as a unit operation covers equipment (e.g., the freezers). As noted above, some therapies may be more sensitive to the freezing process in general. Cell and gene therapies, for example, often have a requirement stipulating they be frozen at a certain rate. Typically, this could be a rate of -1°C (-1.8°F) per minute. If the material is frozen too fast, some of the cells may be damaged; if it is frozen too slowly, toxicity may increase in the cells.

Another risk is cryoconcentration caused by non-uniform freezing, which creates pockets of varied solute concentration. These fluctuations in formulation concentration can negatively impact product quality. Utilization of controlled-rate freezer equipment is recommended to ensure optimal freeze rates and homogenous freezing, in addition to faster freeze/thaw cycling to increase throughput, Figure 2.

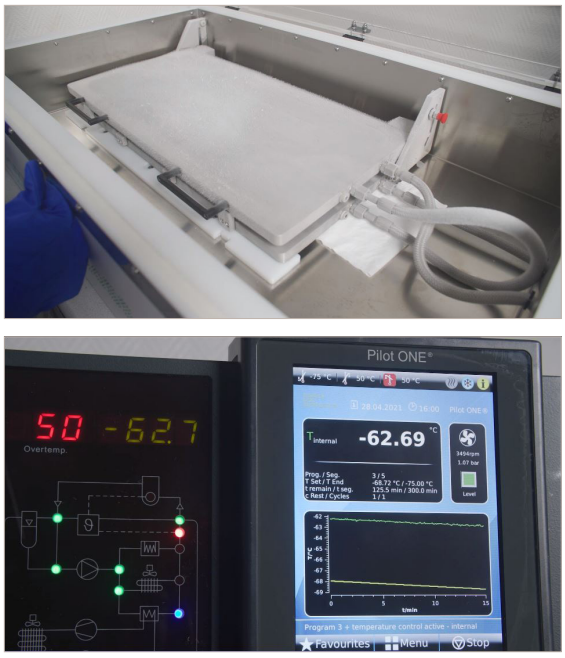

Figure 2. Controlled-rate plate freezer

Once the freezing method is determined, the goal temperature for storage must be considered. Vaccines – for example, proteins and antibodies – typically are stored between the -40°C (-40°F) and -80°C (-112°F) range, but cell and gene therapies are emerging that require liquid nitrogen-level temperatures below -150°C (-238°F). Manufacturer equipment must support the mandated temperature ranges, achieving those temperatures in ways that will not harm the product, and then execute controlled thawing when it is time to remove the biologic from the process.

Sometimes, freezing and frozen storage do not occur at the same place. Or, separate freezers at the same location are used for the controlled freeze process and storage. Occasionally, the same freezers are used for both tasks. Ultimately, this depends on the existing infrastructure available to the manufacturer, and they must plan to accommodate within their capability. In some cases, the manufacturer's capability may not meet demand, so determining their capability early is key to updating their freeze/thaw infrastructure within the necessary timeline.

Step three for manufacturers is the cold-chain service aspect: scale-up and a larger distribution network are likely to require at least one logistics partner trustworthy enough to handle and transport the sensitive products well. This entails both mechanical robustness (i.e., no damaged shipments) and not subjecting the product to temperature excursions. If a biologic's temperature fluctuates even a few degrees, its functionality can be impacted, or variability can be introduced between batches. Instances of such events might include a temperature excursion due to a plane delayed on the hot tarmac, or the mechanical impact of the product being loaded onto a truck improperly. A trusted supply chain partner acts as a buffer against these risks.

HOW ENTEGRIS OPTIMIZES COLD-CHAIN OPERATIONS

Entegris customers – for example, a customer producing a vaccine during the pandemic – typically approach them for cold-chain scale-up following successful Phase 1 approval of their biologic. The process generally starts with a forecast: "These are our projected batch sizes in X months. This amount of time will be spent in evaluation. This amount of time will be spent testing larger sizes. This amount of time will be spent on stability, freeze/thaw, shipping testing, etc."

The more front-end information a supplier partner has, the more helpful to build a successful cold-chain operation – particularly in the process' early stages. For example, the supplier does not have direct contact with the customer's CMOs or CDMOs – they are talking with the end user – so the manufacturer supplying input on those entities is vital. Consider that the CDMO may not have the same freezer, or the same freeze/thaw infrastructure, as the pharmaceutical end user. Deviations must be adjusted to, and it is important for the supply chain partner to have access to suppliers' and other partners' data to aid in planning or designing solutions that maximize the use of equipment and space without sacrificing quantity, quality, or efficacy.

As part of this process, Entegris can demonstrate product compatibility, stability, and scalability with its primary container. In many cases they can offer Aramus™ single-use bag assemblies for cold-chain collection and storage, Figure 3. The single-layer fluoropolymer provides gamma stability with low extractables and leachables (E&L) and has a wide operating temperature range. Further, the bag assemblies, tubing, and connectors can be adapted to a number of single-use system (SUS) configurations.

Figure 3. Aramus single-use bag assemblies

Of course, Entegris can acknowledge and study different materials that have been tested and shown to be stable in these applications. Every product is different, and due diligence requires manufacturers to alleviate concerns and mitigate risks during packaging evaluation, but Aramus assemblies can instill confidence that a viable solution is available. Further, Entegris assigns an application engineer to work directly with each customer in the design, ensuring they understand their process a little better and empowering them to make informed decisions regarding optimal selection of materials and configuration.

This mindset follows the general best practice of manufacturers working as closely as possible with their suppliers in open dialogue protected by the confidentiality of that partnership. Honest conversations need to take place around demand planning, as well as the benefits of a platform end-to-end solution for the process – one that maintains product integrity with no temperature excursion or mechanical damage. The manufacturer wants to ensure the solution they are buying into will work with their existing infrastructure, adapting and growing alongside their own capability. As collaborations that ushered vaccines to market in record time proved, as long as communication and the supplier/manufacturer relationship is strong, scale-up challenges are easier to overcome.

Finally, automation must be acknowledged as an obvious solution to effective cold-chain scale-up. The industry already embraces automation and seeks to implement more: it is consistent, efficient, and cost-effective. Cold-chain operations do offer such opportunity. For example, one can have controlled freezers that can be programmed to run specific temperature-time profiles, monitor ice formation, and connect to other unit operations for better process integration.

Ultimately, automation is an element of process control. For cold-chain operations, it also could include tracking shipping in the distribution network: real-time GPS location, temperature, shock, etc. So, the manufacturer knows exactly where its shipments are and what they have gone through. This provides manufacturers a chance to isolate shipments that may have encountered problems and examine root cause, versus finding out as they are trying to move on to fill/finish operations.

CONCLUSIONS

Understanding the biologic and the materials it contacts, realizing the intricacies of equipment to be used, and leveraging the advantages of different service offerings and partners – these three elements must interact with one another harmoniously to ensure effective cold-chain scale-up. That complex relationship warrants treating cold-chain scale-up as its own unit operation.

Entegris offers each customer a customized, application-specific offering, catering to their needs in each of these elements. They also are able to execute this plan quickly: while lead times vary between three months and a year for materials elsewhere, careful internal planning and investment in their capacity allows Entegris to offer timelines one-half to one-third that range. Add expertise in the broader single-use supply chain (beyond cold-chain) and they are able to adapt and support rapid scale-up for customers exhibiting a range of needs.

Flexibility and speed, design and configuration support, the selection of single-use options, and the turnaround time they offer all set Entegris apart. They are eager to discuss your cold-chain and single-use supply chain challenges, and help you overcome them. To get the conversation started contact the author or visit Entegris online at https://www.entegris.com/en/home/resources/industry-insights/cold-chain-bioprocessing.html.

ABOUT THE AUTHOR

Muhammad Siddiqui is a cold-chain applications engineer for Entegris, Inc. His experience centers on single-use freeze/thaw and cold-chain operations for existing biologics and emerging therapies. In his current role, he works to expand Entegris' fluid management solutions while building industry knowledge and engagement in low-temperature applications. Mr. Siddiqui holds a master's degree in chemical engineering from the University of California, Berkeley with a focus in product development.

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