

ASHP Executive Forum on
COLD CHAIN MANAGEMENT

Resource Guide #3

**PREPARING FOR THE
FUTURE OF COLD CHAIN
MANAGEMENT**

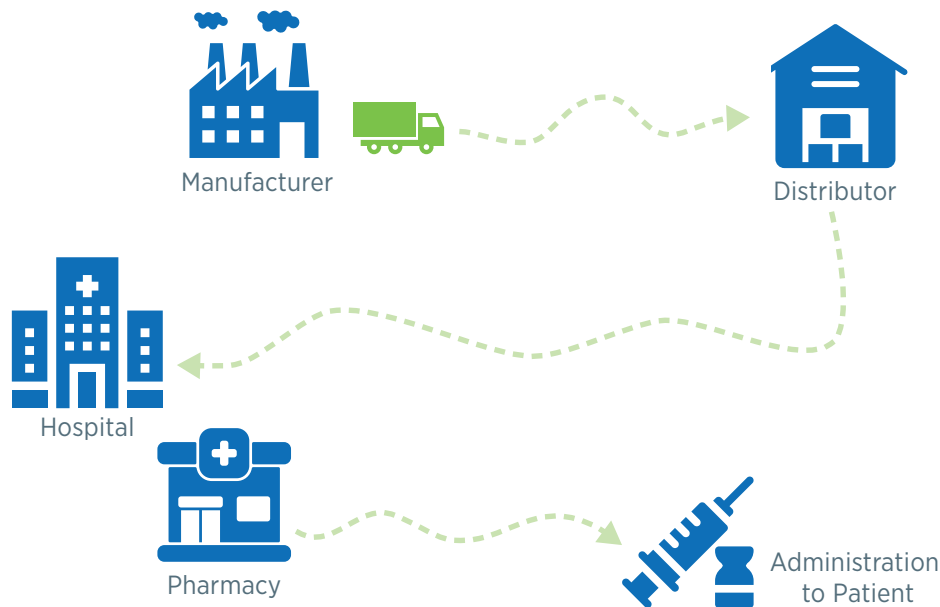


BACKGROUND

Pharmacists play a critical role in product procurement, storage, handling, and transport of medications for hospitals, health systems, and alternate sites of care within their communities. The rapid introduction of medicines requiring precise temperature control, including biologics, compounded infusions, and specialty drugs, will likely expand requirements for unique handling, storage, and transportation needs. Leveraging the expertise of pharmacy leaders in advancing cold chain management and collaboration with all supply chain stakeholders is needed to optimize design and innovation of cold chain processes and supporting

technologies. The importance of cold chain expertise and capacity was amplified by the development of COVID-19 vaccines that required a reliable cold chain — from the point of manufacture to the point of administration — at massive scale. Pharmacists will continue to provide leadership and build upon their expertise in the management of the drug supply chain and its integrity. This initiative is part of the ASHP Innovation Center’s mission to influence innovation, collaboration, transparency, and digital transformation in the safe and effective use of medicines.

Diagram of Cold Chain Stakeholders



INTRODUCTION: PREPARING FOR THE FUTURE OF COLD CHAIN MANAGEMENT

This is the final of three resource guides developed through a series of ASHP executive forums on cold chain management. The first resource guide, *Pharmaceutical Cold Chain Management in Health Systems*, addressed the current state of cold chain management, supportive infrastructure needed for optimal cold chain management, priorities across stakeholders, and pharmacy operations and design considerations.¹ The second resource guide, *Health-Systems Design to Optimize Cold Chain Management*, addressed health-system design elements, including infrastructure and regulatory requirements, risk and mitigation strategies, and excursion management, and included a *Cold Chain Management Self-Assessment Tool* for health systems.² This resource guide, *Preparing for the Future of Cold Chain Management*, looks explores how organizations can prepare for a future with predicted growth in the drugs requiring cold chain management, including those stored at ultra-cold temperatures, as well as leveraging innovations in technology. The March 28, 2023, forum brought together 21 pharmacy leaders representing health systems, specialty pharmacies, wholesalers, distributors, pharmaceutical manufacturers, federal pharmacy, and other stakeholders. The objectives of the forum were to:

1. Review evolving medicines, including biologics and compounded infusions, and the anticipated impact on cold chain requirements (e.g., unique handling, storage, and transportation needs).
2. List recommendations for leveraging technology to close gaps across the supply chain.
3. Identify ways to prepare for new requirements and challenges while future-proofing the cold chain.

COMMONLY USED TERMS

Cold Chain Monitor (CCM) is, generally, a single-use device that monitors the temperature inside a vaccine shipping container. CCMs should be thrown away after being checked. CCMs are stored in a separate compartment of the shipping container.²

Hub-and-Spoke Model is a supply chain distribution model where product is shipped to a regional location (hub) for subsequent distribution to local sites (spokes).

Temperature Excursion is any temperature reading that is outside the recommended range for vaccine storage as defined in the manufacturer's package insert.²

Ultra-Cold Temperature Storage includes deep frozen temperatures (on the order of -40 to -80 °C), and cryogenic (requiring liquid nitrogen; -160 to -180 °C). Some new or in-development vaccines and biologics require ultra-cold storage.³

DRUGS IN PIPELINE: IMPLICATIONS FOR THE COLD CHAIN

To evaluate cold chain management needs for the future, it is important to understand key developments and trends affecting the supply chain. First and foremost, consider that the number of drugs approved requiring cold chain storage has increased over time, and this trend is likely to continue, primarily due to continued approval of new biologics and vaccines, particularly gene therapies, CAR-T, and vaccines. Adding to the complexity, a growing number of advanced specialty therapies, like antimicrobials, cell and gene therapies, require ultra-frozen (as low as -80°C) or cryogenic (as low as -196°C) storage.⁴

These high-cost drugs carry a significant risk of financial loss when subjected to unmitigated temperature excursions. Forty-three percent of the 292 new drugs approved from January 2018 to March 2023 required cold chain storage, and 6% required storage at freezing or below.⁵ While product stability information is provided in product labeling, manufacturers can only provide stability and excursion information for Food and Drug Administration (FDA)-approved preparations and indications, and stability data often evolves, particularly when new products come to market. When COVID-19 vaccines were originally distributed, they required ultra-cold temperature storage, but now they can be refrigerated. While this shortens the shelf life, the change has greatly improved facilities' ability to manage the products and more efficiently administer the vaccines to patients. Unfortunately, there is no central repository for available stability information related to cold chain excursions, and there little standard stability data for new products as they come to the market. Thus, it's time-consuming for organizations to evaluate the potential impacts of known excursions, particularly when multiple products are involved (e.g., when a storage refrigerator breaks down or a prolonged power outage occurs). Manufacturers, distributors, and health systems are looking seriously at their capacity to handle this projected growth and complexity.

In addition to grappling with the need to expand capacity, stakeholders are also concerned about cold chain sustainability, especially when ultra-low



A growing number of advanced specialty therapies on the horizon, like cell and gene therapies, will require frozen, ultra-frozen (as low as -80°C) or cryogenic (as low as -196°C) storage. This will require planning for additional space, monitoring, storage, and shipping considerations.

DRUG INDUSTRY LEADER

temperatures are involved (e.g., dry ice, re-ice). Sustainable solutions for packaging and shipping materials are still evolving, and suppliers need to consider reusable and recycling feasibility for the end user. Forum participants said their organizations valued biodegradability, ability to recycle, and a green commitment but faced challenges sourcing cost-efficient, environmentally friendly products that meet storage requirements. Waste removal costs are also a concern, especially for health systems that are the final destination in the supply chain cycle. Accumulated ice packs, for example, are heavy and can have high disposal costs. Sustainable solutions for packaging and shipping materials are evolving to meet organizational priorities. Finally, as the supply chain itself continues to evolve, packaging will likely need to accommodate longer durations, ultra-cold shipping, or wider external temperature swings during transport. Remote tracking monitors will also likely become more extensively deployed. In a survey of forum participants, almost 20% were unsure whether they were prepared for changes in cold chain requirements over the next five years, and only 6% felt that they were very prepared. Clearly, there is an opportunity to improve health-system preparedness for the future of cold chain management, including exploring the potential benefits of new technology solutions and collaborations with other stakeholders, including manufacturers, distributors, and shipping services.

Freezer and Below: 17 (6%) of the 292 drug approvals* required storage at freezing or below

Freezer	ULT	Cryogenic
Spikevax (vaccine)	Ervebo (vaccine)	Tecartus (CAR-T)
Elzonris (oncology)	Comirnaty (vaccine)	Abecma (CAR-T)
Cytalux (diagnostic)	Zolgensma (gene therapy)**	Breyanzi (CAR-T)
Nulibry (genetic disorder)	Adstiladrin (gene therapy)	Carvykti (CA)R-T
Oxervate (ophthalmic)	Rebyota (antimicrobial)	Skysona (gene therapy)
Jynneos (vaccine)		Zynteglo (gene therapy)

NDA and BLA drug approvals, 2018-2023 YTD

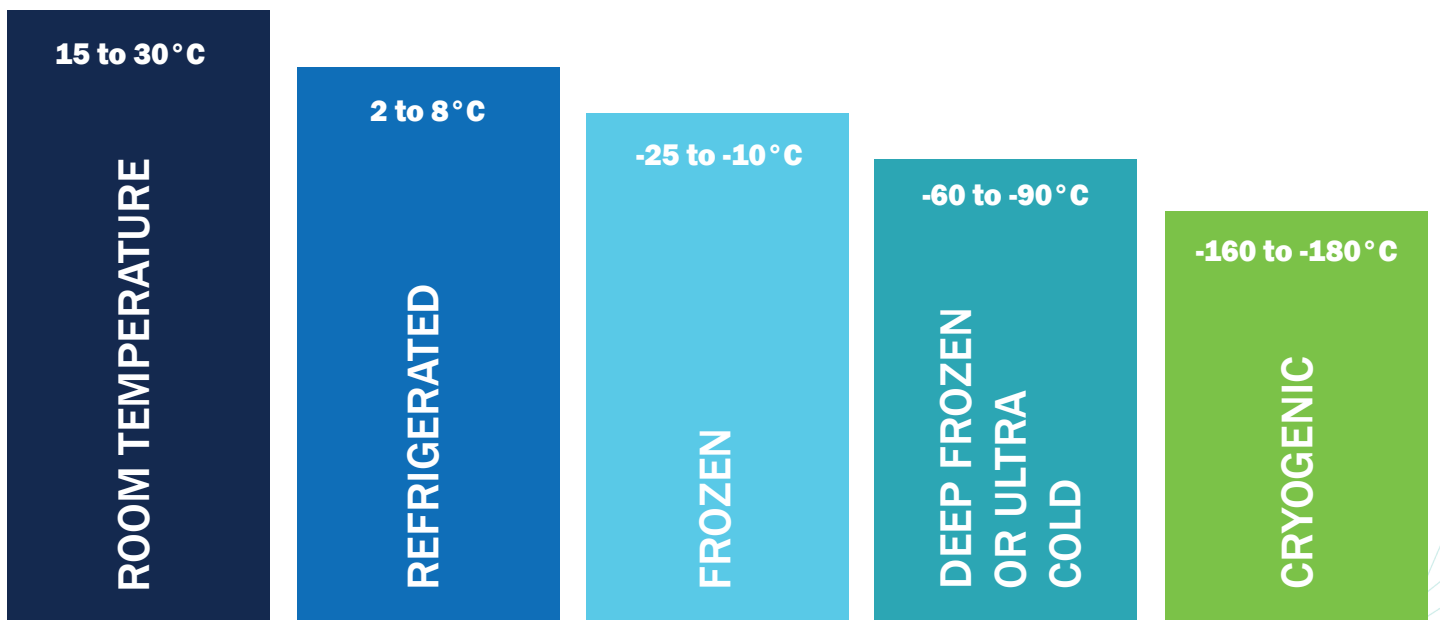
**shipped and delivered frozen; refrigerated upon receipt

<https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022>

<https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year>

<https://online.lexi.com/lco/action/login>

Vizient internal analyses



LEVERAGING ADVANCED TECHNOLOGIES ACROSS THE SUPPLY CHAIN TO MEET FUTURE NEEDS

Key elements of cold chain distribution include transportation, temperature monitoring devices, FDA-approved insulated boxes, and cold packs (e.g., dry ice and gel packs).⁶ Manufacturers and distributors are continually exploring ways to ensure product integrity, and leveraging technology is key. Optimal technologies must integrate transparently across the supply chain.² This improves predictability and, through a collaborative approach to quality improvement, brings a high level of system reliability. Innovative technologies that affect cold chain management, include automated process-oriented tasks, such as temperature monitoring; robotic technology to manage inventory; and shipping and smart packaging innovations. New cloud-based applications provide actionable information, including real-time monitoring of temperature, location, and device integrity, allowing for more timely mitigation of excursions or potential excursions. Collectively, these innovations support a

more efficient, transparent, and data-driven supply chain.⁷ Some advanced technologies leverage predictive modeling and artificial intelligence to trigger an early response that prevents product loss – for example, connecting the product to data on weather emergencies or transportation breakdowns, then rerouting the shipment or replenishing freezer packs. By consolidating cold chain tracking information across the supply chain, stakeholders can be predictive or proactive, rather than reactive.⁸ When considering the supply chain, end-to-end may include the patient. Post-COVID-19, many consumers expect efficient fulfillment of orders, including prescriptions, with products sent directly to the home. Regardless of the technology and its implications, new approaches will be required to meet the increased demand and complexity required for cold chain storage and transport requirements for a growing volume of medications.

Cold Chain Technology and Shipping Innovations

- Temperature-controlled packaging solutions
- Sustainable packaging (recyclable, reusable and biodegradable)
- Real-time monitoring and tracking solutions
- Predictive modeling software (artificial intelligence)
- Ultra-low temperature storage solutions
- Drone delivery technology
- Smart shipping containers

EXPLORING NEW TECHNOLOGIES

Health-system pharmacies, as they evaluate and justify the purchase of new cold chain technologies, must factor in location, available technology infrastructure, implementation and maintenance costs, and risk reduction. Drone delivery technology shows promise but is in the early adoption phase.^{8,9} Implementation barriers to the technology include weather and topography, foliage density, and weight and size capacity, which may limit packaging and product volume. These limitations may affect the ability to attain required economies of scale. If the local topography is suitable, drone technology may be an alternative to general transport of drug products across the health-system campuses.

Drone used by Novant Health ⁸



Cold chain technologies aren't yet fully interoperable across stakeholder systems and thus haven't replaced manual data entry processes. When evaluating new technology, organizations should consider:

- How the technology supports or automates regulatory and accreditation compliance requirements
- Technology infrastructure (e.g., ability for technology to integrate data)
- Ability to automate routine tasks (e.g., temperature monitoring devices)
- Ability to predict excursions or provide real-time data (e.g., supports more proactive vs. reactive approach)
- Physical plant/physical infrastructure (e.g., hub-and-spoke distribution system, space requirements, geography)
- Benefits of avoiding or mitigating the cost of product loss
- Potential to prevent delays in patient care or harm

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*We began to work with **drone technology** during the COVID-19 pandemic, to connect our central hub logistics center to other locations throughout the health system to move PPE, then we tried to figure out how it might be used for drug distribution within the system or prescription delivery.*

HEALTH-SYSTEM LEADER

CLOSING THE GAP: SUPPLY CHAIN FACES THE FUTURE OF COLD CHAIN

Forum participants identified several challenges to future-proofing the cold chain. First, concerns are mounting about the amount of space that needed to store the increasing number of temperature-sensitive products. Second, sustainable solutions are needed for packaging and shipping materials.



At the end of the day, you can have a molecule that cures everything, but if we can't get it to the patient, it doesn't matter.

PHARMACEUTICAL MANUFACTURER

Lastly, technology may have limitations based on the current infrastructure. Although some organizations can integrate data across systems, others are limited by multiple, disparate systems or interfaces that require manual data entry. Recommendations to strengthen technology benefits and opportunities for future-proofing the cold chain and closing these gaps include:

- Stakeholders should support aggregation of data across the supply chain, including tracking information and excursion data that make it possible to be more predictive and proactive than reactive.
- Suppliers and health systems should consider how new technologies can track and document product disposition and integrity across the supply chain, supporting regulatory requirements such as Drug Supply Chain Security Act.
- Technology and data should be integrated and interoperable across platforms to allow stakeholders to react and respond to an issue in real time.
- New technology devices (e.g., SmartTote and TempTrace) should allow for seamless integration and monitoring of cold chain integrity and serve as deterrents to diversion.

- Health systems should evaluate new technologies in the context of their infrastructure. For example, drone delivery may not be ideal to ship products directly to patients, but the technology may have utility to transport drugs from a central fill location to sites within the system.
- Stakeholders should develop strategic partnerships to optimize the benefits of new technology, including the sharing of critical data that help stakeholders make better business decisions around risk mitigation.

Manufacturers and distributors are responding to the cold chain challenges. The industry learned a lot during the COVID-19 pandemic about vaccine storage requirements, challenges getting vaccine into patients in a timely manner, and the potential for product loss and waste when the process is not well managed. Manufacturers are focused on the new drug pipeline and urge ongoing dialogue with health-system pharmacists, who understand these issues, the implications for patient care, and the need to deliver viable product to the patient. Wholesalers also emphasize the importance of strategic partnerships as they redefine their facilities, processes, and technology to meet expanding cold chain needs while partnering to gain insights and make better decisions about risk and risk mitigation. Manufacturers and wholesalers are also committed to sustainable

packaging solutions, which remain a challenge.



As an integrated delivery network, we're really looking for integration for real-time action. Ideally, we have a single system, but short of that, solutions that can integrate and centralize data so our disparate systems can talk and allow us to react and respond in real-time.

HEALTH-SYSTEM PHARMACY LEADER

CONCLUSION

A growing number of complex biological drugs and infusion products requiring temperature-controlled storage and transport — including ultra-cold storage— are coming on the market. That trend is likely to continue, and it will require planning and collaboration among all stakeholders across the supply chain. Challenges include storage space and devices to manage the projected growth; the ability to integrate data and generate timely, actionable information; and a need for sustainable packaging solutions. Stakeholders can leverage new technologies and strategic partnerships to address these gaps and ensure that health systems are prepared for the future of cold chain management.

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This resource guide is a product of the final of three invitation-only executive forums on cold chain management. The first forum focused on Cold Chain Management 101 and laid the foundation for current state that exist in hospitals and health systems. The second forum focused on health-systems design to optimize cold chain management including cold chain excursion management, regulatory compliance and considerations, and facility and equipment strategies. This event focused on the future state including advancements in technology and innovation. ASHP looks forward to working with decision-makers and members of the interprofessional team, to continue to effectively manage supply chain needs, as well as influence regulations and technologies as they evolve. **The executive forums on cold chain management were made possible through the support of Cold Chain Technologies, Inc.**

