ASHP Executive Forum on
COLD CHAIN MANAGEMENT

Resource Guide #1

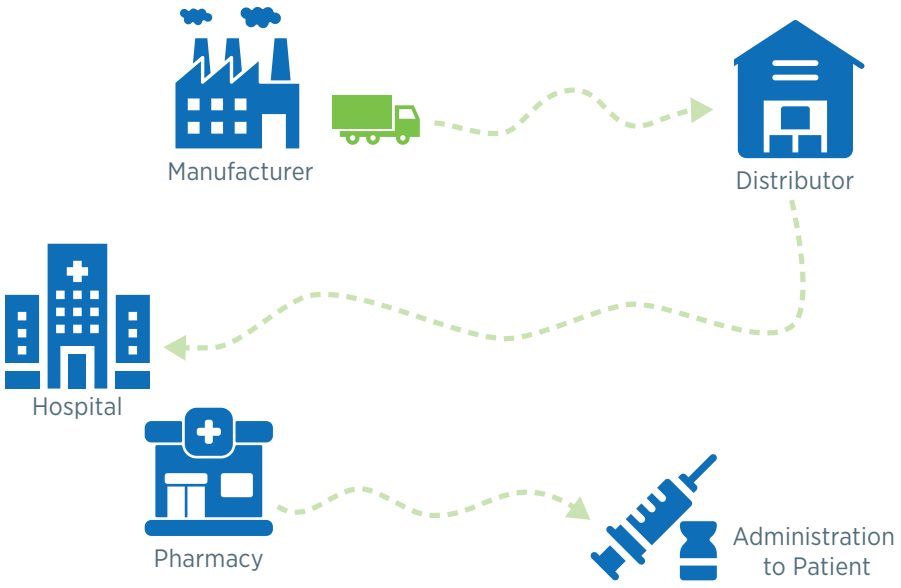
PHARMACEUTICAL COLD CHAIN MANAGEMENT IN HEALTH SYSTEMS

ashp® Innovation Center

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



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).

Mean Kinetic Temperature (MKT) is the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variation. It is not a simple arithmetic mean (see Good Storage and Distribution Practices for Drug Products <1079>).[3]

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

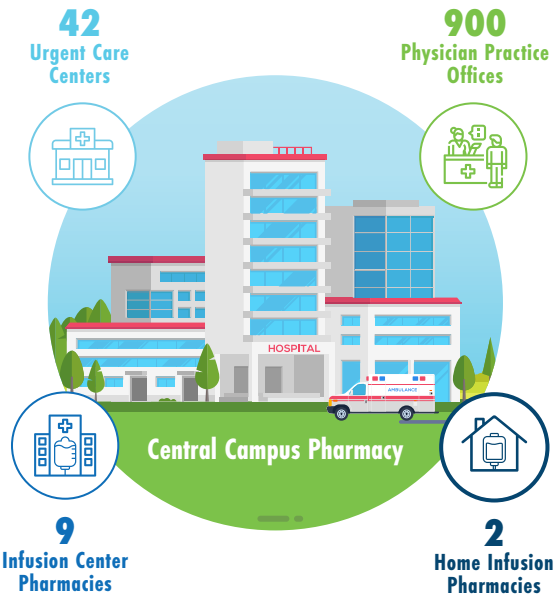
INTRODUCTION: THE CURRENT STATE OF PHARMACEUTICAL COLD CHAIN MANAGEMENT IN HEALTH SYSTEMS

The first of three executive forums to examine issues and recommendations related to cold chain management in health systems was held on April 19, 2022. Twenty-five pharmacy leaders and experts representing pharmaceutical manufacturers and distributors, group purchasing organizations, technology solutions, and global supply chain management participated in a guided discussion focused on the current state, including challenges, lessons learned, and strategic priorities. The objectives of this initial forum were to:

- Describe the current state of cold chain management, including strategic imperatives.
- Discuss barriers and supportive infrastructure needed for optimal cold chain management.
- Identify knowledge gaps and the need for information and implementation support.
- Develop recommendations for health systems, industry, manufacturers, distributors, and cold chain suppliers.

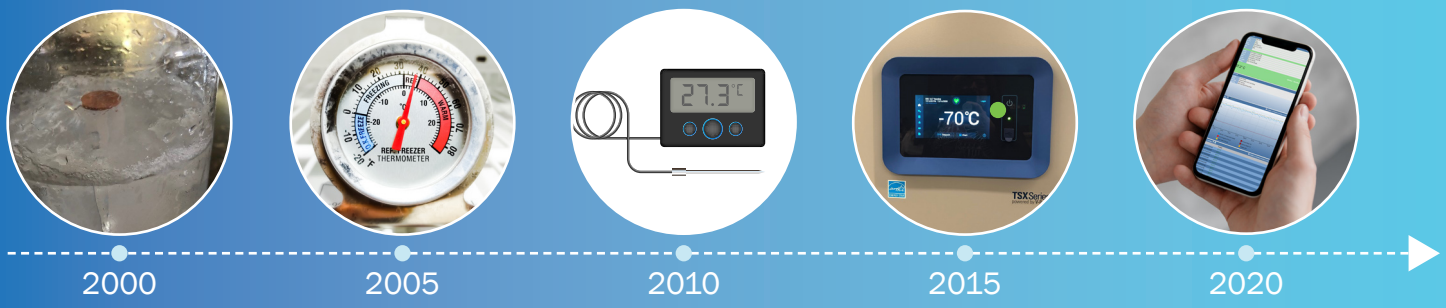
Subsequent forums will explore health-systemization of cold chain management and future directions. The April forum began with an overview of logistics and planning that are required when a pharmaceutical product must be stored and transported at a specific, low temperature throughout the supply chain (i.e., "the "cold chain"). It is critical to prevent temperature excursions throughout handoffs and ensure temperature is controlled and monitored to ensure that product integrity is maintained. At some large health systems, there can be hundreds of drug storage locations that require precise temperature control

Figure 1. Locations Requiring Cold Chain Storage Monitoring at One Large Health System



(Figure 1). Variances can result in delays in patient care, ineffective therapy, financial losses, and significant manpower resources to investigate, report, and mitigate incidents. Forum participants indicated that the primary driver for investing in cold chain management at their organization was risk mitigation (e.g., cost of product loss) and regulatory or accreditation compliance. This aligns with the findings from an IQVIA Institute study that cold chain-related issues cost the pharmaceutical industry as much as $35 billion annually, including product losses[1]. As the number of cold chain products and the product cost has increased, there has also been advancement of technology to monitor the cold chain, with a shift from manual checks and documentation to remote,

Figure 2. Adoption of Cold Chain Temperature Monitoring Technology in Health Systems



electronic monitoring and alerts *(Figure 2)*. The growth in the volume of products requiring cold or ultra-cold storage has also impacted pharmacy workflow and design. Considerations include storage space and capacity, system redundancy and backup, transportation to remote locations, mail delivery, and reporting and investigating variances (Table 1). Finally, during the forum, participants shared ideas and explored opportunities for action on their near-term strategic priorities related to cold chain management:

- Create systems that build in success vs. focusing on individual occurrences (e.g., conduct a failure mode and effects analysis).
- Conduct a gap analysis and develop a risk mitigation framework (e.g., track cost of product loss, apply continuous quality improvement approach).
- Ensure regulatory and accreditation compliance (e.g., documentation of excursions and action plans).
- Build in system redundancies (e.g., generator backup, inventory storage limits within a single unit or site).
- Ensure timely end-use access to products (e.g., health-system goal to have COVID-19 vaccine available in every clinic for patients).
- Develop systems to monitor performance and support continuous improvement along the entire supply chain.

Table 1. Pharmacy Operations and Design Considerations

Temperature Monitoring Plan
• Integrated monitoring
• Recording data
Cold Chain Monitors
• Remote monitoring
• Active alerts
• Cost-effective
Safety and Risk Mitigation
• Electrical wiring for non-interrupted service
• Dry ice handling and disposal
• Location and equipment redundancy
• Action plans
Storage Space
• Refrigerated medications
• Frozen medications
• Shipping/transport supplies (e.g., gel packs or dry ice for shipping)
Storage
• Deep freezers
• Refrigerators
• Transport
Operational Considerations
• Logistics for receiving medications (e.g., receiving cold storage, split orders to different days)
• Ordering and distributing (e.g., Just-in-Time to minimize waste)
• Transport to remote locations (e.g. storage containers and packaging)
• Storage options and monitoring for remote locations

COLD CHAIN IMPACT ON HEALTH SYSTEMS

Health-system pharmacies have significant cold chain management challenges to meet, including ensuring consistent management and monitoring of product storage temperatures across the organization, the need to meet regulatory compliance requirements across disparate settings, and the risk that temperature excursions will lead to loss of medications or a negative impact on patient care. The complexity of addressing these issues became more apparent when the COVID-19 vaccine was deployed and was required to be maintained at sub-freezing temperatures from the time it left the manufacturer to the time it was prepared for administration to the patient. All stakeholders were challenged with how to maintain the integrity of the product throughout the entire cold chain and how to accurately identify and manage temperature excursions. Over 90% of respondents of an informal ASHP survey of 300+ bed hospitals indicated that, during the pandemic, they had to acquire additional cold space storage (e.g., refrigerator and freezer); an average of four additional devices were purchased. Over 75% reported they had to quarantine drug product related to a cold chain issue (e.g., known or suspected temperature excursion), with over 50% reporting product loss, and over half of those resulted in a non-recoverable financial loss. All participating stakeholders acknowledged that even a single failure within the cold chain can have a significant impact on resources, and in some cases, patient care, and every variance should be seen as a quality improvement opportunity. Greater transparency and collaboration among all cold chain stakeholders will help to more effectively identify gaps and opportunities for improvement. Forum participants made several observations about the current state of cold chain management:

- Over the past two years there has been a significant investment in cold chain infrastructure across all sectors.
- The pandemic was a driver that both stretched and expanded resources, including storage space, infrastructure, and experienced staff.
- Acute events showcased the importance of emergency preparedness including inventory management and consolidation of product.
- Manufacturers and wholesalers are constantly working to improve shipping, storage, handling and stability of products.
- There is no best practice for managing documented excursions, and the process is often trial and error and product and manufacturer specific.
- There is a lack of understanding and consistency of practices across all stakeholders when cold chain incidents occur; this makes it difficult to validate product integrity before and after handoffs.

> ***Awareness of the challenges*** *is the first step to understanding what is happening across handoffs and to share information with each other to understand where the risks are and where we can make improvements. I don't know that there's always a right answer, but there is a "continuous improvement" answer.*
>
> **INDUSTRY PARTNER (ANNOTATED)**

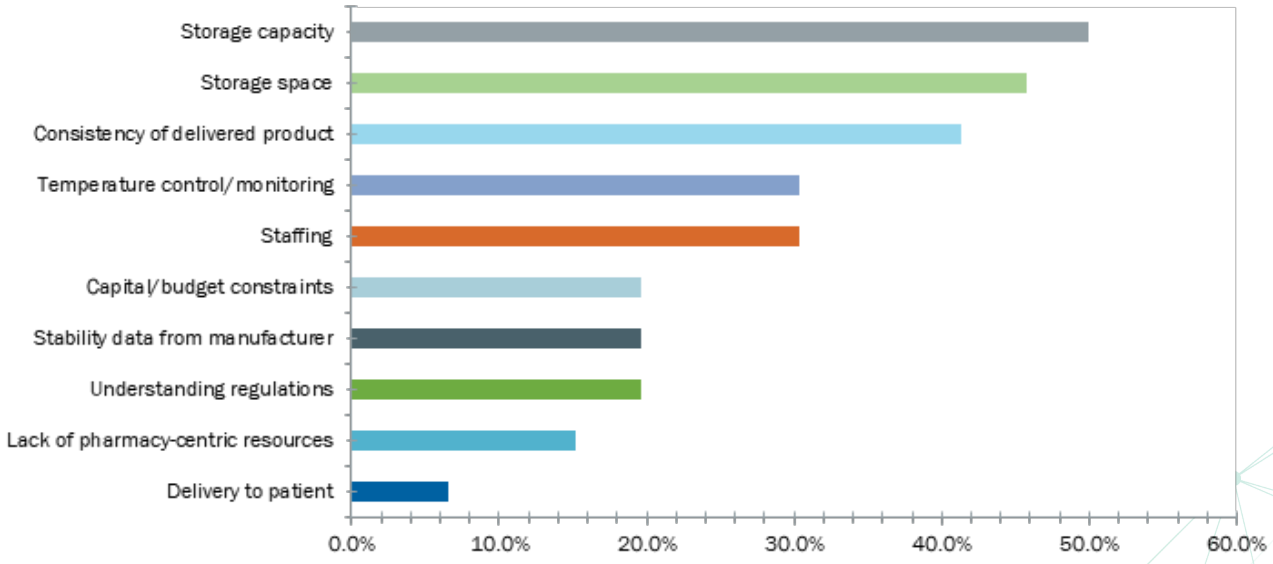
COLD CHAIN CHALLENGES

While there are challenges within individual segments of the cold chain, there is lack of collaboration and standardization across these segments. For example, from an industry perspective, the wholesaler may have different requirements and monitoring technology from the manufacturer. These stakeholders have to consider their ability to support other segments and the cost to provide that support. All stakeholders said that they were willing to go "above and beyond" to make sure they ultimately support the clinical setting for timely access of product to all patients. To overcome these challenges, particularly during the COVID-19 vaccine deployment, it was critical to leverage the expertise of existing systems and educate others about processes and options. At the health-system level, survey respondents indicated that top challenges were storage capacity and storage space for cold chain devices and equipment, consistency of delivered product, and staffing (Figure 3). Forum participants cited several additional challenges, which were also seen as opportunities for collaboration and improvement:

- A lack of transparency and access to real-time data across segments of the cold chain (e.g., how long was the product out of storage, what was the temperature) creates challenges for addressing temperature excursions (e.g., each stakeholder is monitoring differently, so there is no way to validate what occurs before or after handoffs).
- A major challenge is transporting products requiring ultra-low temperature (ULT) storage to smaller volume or offsite, more remote locations.
- There is inconsistent interpretation of USP Chapter <695> and the application of MKT when assessing temperature excursions.
- The principles of cold chain integrity don't always reach the end user, and thus, they may not be as familiar with what is required.
- Variability across manufacturer, wholesaler, and provider sites creates disconnects and uncertainty when issues occur.
- Efficient use of space and recycling of cold chain packaging are concerns.

Figure 3. Top 3 Challenges Related to Cold Chain Management in the Past Year

(Health-system pharmacies >300 beds)



COVID-19 VACCINE DISTRIBUTION

Industry Rises to the Challenge

The development of the Pfizer–BioNTech COVID-19 vaccine posed several complex challenges in distributing the vaccine at ultra-low temperatures to sites around the world. Members of Pfizer's vaccines medical affairs team shared Pfizer's experience successfully navigating distribution and cold chain requirements in response to the COVID-19 pandemic.

Vaccine development and production of billions of doses to meet global demand included the proper tooling and scaling up of manufacturing sites and ensuring product stability for use in clinical settings. To sustain production, minimize wastage, and for vaccines to reach target populations, the creation of an efficient and resilient vaccine supply chain was imperative. This included the development of coordinated end-to-end supply cold chain requirements assisted by temperature monitoring technologies from the point of manufacture, transportation to distribution centers, and ultimately to immunization sites. It was important to leverage Pfizer's extensive global supply chain and cold chain management experience and collaborate with partners to ensure access to populations in urban and rural areas, including underserved regions.

Pfizer's COVID-19 vaccine distribution is built on a flexible, just-in-time system, which ships the frozen vials direct to the point of vaccination. To accomplish this, innovative solutions were required to meet global demand, including acquiring ULT freezers to store manufactured doses on a massive scale configured as "freezer farms" (Figure 4), developing a temperature-controlled thermal shipper using dry ice with flexible packaging options (Figures 5 and 6), and implementing real-time monitoring of temperatures and location via GPS enabled thermal sensors. Upon receipt of the vaccine, points-of-use sites are provided a disposition report ensuring product quality.

Pfizer has stated they remain committed to continuous improvement, conducting ongoing stability studies, and improving formulations to optimize storage conditions for the vaccine.

Figure 4. Pfizer "Freezer Farm"

Courtesy of Pfizer, Inc.

Figure 5. Temperature Controlled Thermal Shipper

Courtesy of Pfizer, Inc.

Figure 6. Dry Ice and Flexible Packaging Options

Courtesy of Pfizer, Inc.

ADDRESSING BARRIERS TO COLD CHAIN OPTIMIZATION

Forum participants noted several barriers to optimizing the cold chain, and agreed that the problem is multifactorial. Some common issues impacting optimization include the pace of implementation, staffing demands, financial constraints, and a general lack of knowledge. Wholesalers have been dealing with cold chain issues and have made an effort to educate health-system staff about cold chain processes and packaging.

> *We now have knowledge, and **with that knowledge comes power**; the relationships created have been critical and we need to continue to build on them and share that knowledge.*
>
> **HEALTH-SYSTEM PHARMACY LEADER (ANNOTATED)**

For example, thawed ice packs do not necessarily mean there has been a temperature excursion. Ideally, everyone along the supply chain would know how long the product was out of storage, where, and for how long. Investigating potential temperature excursions is labor-intensive, and there is not a standard way to verify and report occurrences, in part, because the processes vary across organizations. Tools are now available and getting more affordable to scale, but there is still a significant gap where we are today vs. a future that takes full advantage of technologic capability. Another barrier is space and equipment constraints. Health-system administration has been very willing to approve capital purchases, but there are often other related constraints related to space in smaller clinics and practices and ensuring adequate space and infrastructure (e.g., backup power supply). There is also a need for more depth of expertise; most health-system pharmacists have learned through on-the-job training, but there needs to be more staff knowledge in the clinical and remote sites. As health systems strive to optimize the cold chain, there will need to be education support, such as certificate programs, and all stakeholders should contribute their expertise. Forum participants felt, though, that it was most important to implement training in systems design. This can be accomplished through dissemination of lessons learned and stronger collaboration with industry partners. Finally, to support the expected growth of products requiring cold temperatures, stakeholders across the supply chain segments must build on those existing relationships. Some key recommendations for advancing cold chain optimization across segments include:

- Bring USP into future conversations to assist with interpretation and applicability to new situations and technologies.
- Educate everyone involved in the chain on their processes as well as an understanding of others' needs and requirements.
- Collaborate for more transparency, alignment, and cooperation across the stakeholders.
- Health systems should leverage partnerships with industry to help address challenges and extend learning and support to clinical settings.
- Develop educational sessions, web resources, and other programs to build expertise.

> ***Growth has been a barrier** and has resulted in a dilution and lack of expertise at end user sites. There is much variation in cold chain logistics, and it's getting more complicated, and will be more difficult to keep up as the need grows.*
>
> **HEALTH-SYSTEM PHARMACY LEADER**

A WORD ON PREPAREDNESS

Forum participants felt that addressing known challenges and preparedness was core to cold chain optimization. Lessons learned from past events like Hurricane Ida can be applied to preparedness for similar events that disrupt the supply chain, cold chain included. Recognizing that disruptions may not always have advance notice (as with hurricanes), preparedness must address operations leading up to and during an acute event as well as infrastructure challenges that occur afterward (e.g., power and access). Minimizing product loss while maintaining access to patient care requires careful planning. Some key considerations are listed in Table 2.

> *If there is a major failure that involves multiple products, we have to contact several manufacturers and it's an "all hands on deck" approach.*
>
> **INDUSTRY PARTNER (ANNOTATED)**

Table 2. Considerations for Cold Chain Preparedness

Design systems to reduce losses

- Know where your drugs are! Where are they located and how much inventory is in each of those refrigerators?
- Set inventory limits for each storage unit (e.g. one site limits inventory to $10,000/small refrigerators in clinic locations).
- Ship in smaller quantities.

Design systems for redundancy

- Move away from double-wide to single-wide refrigerators.
- When inventory is high, have the option to move drugs to regional hubs/warehouses.
- Ensure back-up to back-up generators.
- Consider power supply needed for additional storage requirements.

Design systems and processes using a holistic approach

- Supply smaller sites/clinics with product "just-in-time".
- Work with suppliers to stagger deliveries to streamline receiving challenges.

KEY TAKEAWAYS AND REFLECTIONS

The pandemic accelerated the implementation of the cold chain infrastructure across all segments of the supply chain, and resources grew at unimaginable rates due to the urgency. Manufacturers produced product with incredible speed and developed an end-to-end distribution system with built-in accountability and high reliability. Transportation companies and wholesalers shared their existing knowledge to ensure a sustainable solution. Within health systems, pharmacies became the "go-to" resource for cold chain management, since access to the vaccines and other drugs were so important during the pandemic. The increase of capability and knowledge will make things more nimble in the future, and newly formed partnerships will allow for scale and innovation.

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This resource guide is a product of the first of three invitation-only executive forums on cold chain management that began in spring 2022 and will continue to spring 2023. As you have read, the first forum focused on Cold Chain Management 101 and laid the foundation for current state that exist in hospitals and health systems. The next event this fall will focus on health-systems design to optimize cold chain management including cold chain excursion management, regulatory compliance and considerations, and facility and equipment strategies. The third event will focus 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 be 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.**

COLD CHAIN TECHNOLOGIES