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Managing Cold Chain Distribution Across the Global Supply Chain: Trends and Regulations

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Supply chains now span the globe and are increasing in complexity as organizations move away from regional business models to manufacturing and distribution on a world scale. A critical byproduct of good manufacturing practice (GMP), an unbroken cold chain ensures product safety, efficacy and overall quality for patients. The need for regulations, industry standards and service providers that can support the cold chain process has grown as fast as the asset value of biologics and new drug delivery systems has increased. While it would be ideal to have one reference standard and best-practices approach, there is no magic bullet. It is important to understand what regulations and industry practice standards do exist in order to craft a practical, manageable approach to a secure and consistent cold chain.

Cold Chain Management

Cold chain management and logistics is a specialized concentration within supply chain management that utilizes temperature controlled transportation and storage and distribution systems to ensure the product remains within its recommended conditions. A cold chain management program is meant to:

- Ensure the appropriate storage and handling conditions (temperature) are maintained throughout the cold chain.
- Document the storage conditions (temperature) throughout the cold chain.
- Maintain the product safety and integrity throughout the cold chain (temperature, counterfeiting).

The basic elements of a pharmaceutical or biologic cold chain are shown in *Figure 1*.

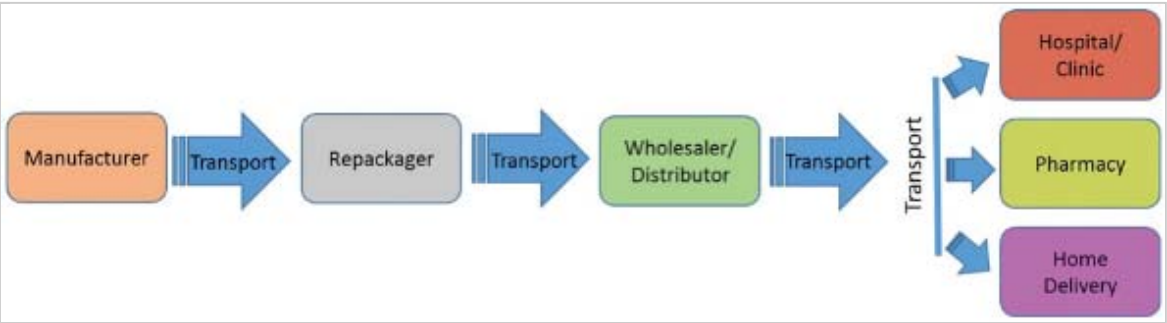

Figure 1.

Establishing an effective cold chain strategy requires the thoughtful integration of cold chain requirements starting with product design and extending to environmental control during transit. Integrating Quality Risk Management (QRM) principles at strategic points within product development is the best way to anticipate downstream cold chain challenges.

Best-in-class organizations undertake primary packaging studies as the first step in answering the larger product stability and environmental label claim requirements. Framing this activity as an integral part of the cold chain design activity rather than perceiving it as a strictly product development activity allows commercial considerations to be included in the product design discussion. This holistic view provides the greatest opportunity for defining any subsequent commercial cold chain alternatives, such as shipper design, active vs. passive container design decisions, and country-specific regulatory requirements. The key elements of some of the major activities that can influence an effective governance strategy are shown in *Figure 2*.

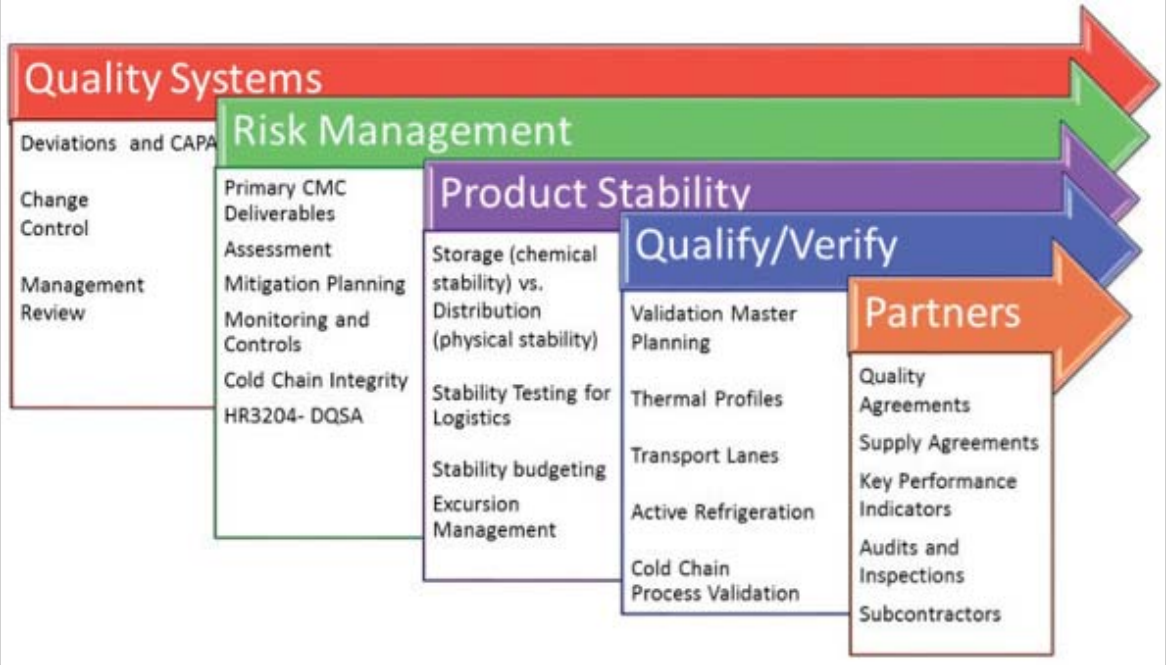

Figure 2.

Regulatory Considerations

The drug sponsor takes primary responsibility for ensuring that the product is fit for use. Specifically, manufacturers of cold chain products have direct control over the correct storage and handling of their products from the start of production through dispatch from their main supply warehouse until the products reach the first point of shipment. This point may be a local operating company, wholesaler, or a hospital. However, while accountable, the drug sponsor can only have an indirect influence on cold chain compliance. The drug sponsor may indicate how the products should be stored and handled based on evidence from preclinical studies and basic knowledge about therapeutic drug physico-chemical properties and requirements. An effective cold chain strategy must also recognize when responsibility lies with a support services component of the supply chain.

Specific compliance requirements for establishing an effective cold chain structure and governance strategy are based upon a combination of regulatory requirements defined by the corresponding regulatory body such as FDA, EMA, WHO, Health Canada, etc. However, industry best practice guidances from organizations such as the International Safe Transit Association (ISTA), United States Pharmacopeia (USP), International Air Transport Association (IATA), International

Committee on harmonization (ICH), and the Parenteral Drug Association (PDA) offer important, practical information on the details and considerations required.

Product Stability

ICH

Understanding the impact of environmental variation on a product's safety and efficacy is a prerequisite to establishing a cold-chain strategy. ICH Q1A (R2), which addresses stability testing of new drug substances and products, is a central industry best practice for building an effective stability program. This data will be used to understand the impact, considering the magnitude and duration of temperature excursions that could occur in the distribution process. Data derived from intermediate and accelerated environmental conditions can be used to determine the potential impact of short-term excursions that could occur in the shipping and distribution process.

Packaging Design and Qualification

USP

The United States Pharmacopeia (USP) 39 chapter 1079 describes "Good Storage and Shipping Practices" with guidance for handling cold chain pharmaceutical products. This chapter provides the requirements for ensuring a product's "identity, strength, quality, and purity" across the entire distribution channel - from manufacturer to end user covering the handling and storage of products in warehouses, during transit, and in pharmacies. This chapter states: "Operational and performance testing should be part of a formal qualification protocol." Thermal testing qualification may be performed using a validated controlled temperature chamber or actual transit testing using the expected transport method and shipping lanes (from origin to destination). Certified test labs use validated environmental chambers to simulate the ambient temperature that the package may encounter using standard profiles that simulate the transit of the package through the distribution channel with changes in temperature and duration. The profiles are established by the International Safe Transport Association (ISTA) and cover both land and air transport of various times and package configurations. Detailed test reports are obligatory to demonstrate support of the regulatory requirements.

ISTA

The ISTA organization focuses on the specific concerns of transport packaging. ISTA is the leading industry developer of testing protocols and design standards that define how packages should perform to ensure protection of their contents during the ever-changing risks of the global distribution environment. ISTA 2 provides the requirements and standards protocols for environmental testing including temperature, pressure and humidity.

Transportation and Monitoring

PDA

The Parenteral Drug Association (PDA) is an industry educational organization that provides detailed guidance regarding activities in drug development in technical reports available to its membership. Each report deals with specific technical, compliance, and monitoring requirements for a particular activity within drug development. Two cold chain management guidances pertain to establishing a cohesive cold chain strategy and governance structure: PDA Technical Report No. 39, revised 27: "Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment" (Suppl., vol. 61, no. S-2); and PDA

Technical Report 46 Last Mile. TR39 provides a very detailed discussion of all the requirements of a cold chain management program from package design and qualification through good distribution practices. TR46 focuses upon good distribution practices of the final product.

IATA

The International Air Transport Association (IATA) is the trade association for the world's airlines, representing 260 airlines and 83 percent of the total air traffic. IATA supports many areas of aviation activity and helps formulate industry policy on critical aviation issues. IATA provides several essential elements specific to cold chain requirements. The IATA has published a temperature control regulations (TCR) guide designed to help stakeholders involved in the transport and handling of pharmaceutical product to safely meet the requirements. The TCR defines industry best practices for drug manufacturers, ground handlers, freight forwarders and airlines. All healthcare temperature sensitive products require the IATA "Time and Temperature Sensitive" label. This label is specific to the healthcare industry and must be affixed to all shipments booked as time- and temperature-sensitive cargo to indicate the external transportation temperature range of the shipment. It is the responsibility of the shipper (or designated shipper's agent by service agreement) to ensure that the label is applied properly.

Cold Chain Management Trends

1. Regulation is Increasing

As the value of new drug therapies and their sensitivity to storage conditions has escalated, one might argue that drug manufacturers do not need any additional incentive to ensure environmental control. For years most countries require that pharmaceutical drug products remain within filed temperature limits. However, the EU's guidance on Good Distribution Practices has extended this requirement to include transportation. While not required in the U.S., we anticipate a similar requirement and many organizations have already adopted temperature-controlled transportation as part of their current cold chain strategy. Biologics are not the only sector driving this practice: even controlled room temperature labeled products require refrigerated transport vehicles to minimize the potential for temperatures excursions.

2. Active vs. Passive Shippers

As logistics become more complex the risk profile of new drug therapies has prompted a shift toward greater environmental control. Passive shippers have been the method of choice for many years. Passive shipping configurations are manufactured systems that are typically insulated with polystyrene, polyurethane, or vacuum insulated panels. Many have been pre-qualified to hold a particular temperature for a certain amount of payload capacity for a specified period of time. With these types of configurations, the shipper uses gel packs or similar materials to maintain the desired temperature. On the other hand, active shippers are powered by electricity and/or battery. Active shipping configurations are considered to be more secure than passive systems because units lock and are never opened during transport. As a result, this design helps reduce the risk of theft and may help maintain regulatory compliance. However, they have the disadvantage of requiring reverse logistics, meaning the containers must be returned to be reused adding cost and complexity to the logistical planning process.

3. Training Remains a Big Issue

With increasing regulation, the compliance component becomes even more critical. Training has always been a large part of cold chain management. To facilitate this organizations such as IATA provide a checklist for ground handlers and airlines to use to ensure the minimum verifications are conducted during the transport.

4. Increased Logistic Outsourcing

Cold chain performance is subject to the same pressures as normal supply chain process to push performance and drive down costs. Many pharma companies have turned to third party logistics (3PLs) firms that are incentivized to make the necessary investments in technology, infrastructure, and systems to drive continuous improvement and gain a competitive market edge. Specialized capabilities such as Automated Search and Retrieval Systems (ASRS) and in-situ x-ray verification of product are examples of tailored specialized capabilities that some 3PLs have adopted to meet the evolving demands of the cold supply chain.

Conclusion

As the value and criticality of life saving drug therapies escalate, regulatory requirements are moving toward closer control over every facet of the cold chain. Even with the disparity in formal requirements among different markets, drug manufacturers and 3PLs are gravitating to the most conservative requirements to drive standardization and ultimately efficiency. With the informal adoption of more stringent requirements, the ability for each piece of the cold supply chain to comply with industry best practices will be challenged. Training will continue to be an issue as ground crews, freight forwarders, and airlines navigate the confusion between absolute requirements and desired practice. Industry organizations such as IATA have attempted to drive standardized work through the use of checklists for freight forwarders and airlines to follow, however the reality is that the ability of these ground teams to stay on top of these responsibilities remains problematic. The success metrics of today's cold chain are at best a moving target with formal and informal regulation complicating today's global supply chain. Collaboration among external service providers could provide the foundation for future compliance risk reduction and potential business success.

Bikash Chatterjee *has guided the successful approval of over a dozen new pharmaceutical and biotech products within the U.S. and Europe and developed and transferred products and processes to satellite operations and Contract Manufacturing Organizations over much of his 30-year career. He has extensive experience with design and implementation of systems to satisfy requirements for ICH Q8, Q9, and Q10 as well as e-pedigree and the application of risk-based approaches in the area of validation. Mr. Chatterjee is a member of the USP National Advisory Board and is the Past-Chairman of the Golden Gate Chapter of the American Society of Quality. He is the author of "Applying Lean Six Sigma in the Pharmaceutical Industry" (ISBN: 978-0-566-09204-6). Mr. Chatterjee holds a B.A. in Biochemistry and a B.S. in Chemical Engineering from the University of California at San Diego.*

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