

## PHARMACEUTICAL COLD CHAIN: A Gap In The Last Mile

### Part 1. Wholesaler/Distributor: Missing Audit Assurance

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#### INTRODUCTION

It is well known in the industry that many biologics and other pharmaceutical compounds can be damaged with excessive heat or freezing, as evidenced in pharmaceutical manufacturer's stability studies, resulting in reduced efficacy. Unless authorized by the pharmaceutical manufacturer on a formula and packout basis, distributors delivering medications to the hospital, clinic, or retail pharmacy must maintain the label temperature; therefore, the packaging needs to maintain product temperatures and accommodate ambient temperature/humidity and weather changes.

Unfortunately, a recent gap analysis performed by Thermal Packaging Solutions (TPS) found packaging that presents

the opportunity to almost certainly freeze some of the container contents. In this case study with Brigham and Women's Hospital (BWH), a 788-bed academic medical center, packouts sent by one of the top three U.S. wholesaler/distributors (W/D) were observed.

Responsibility for the quality of all medications supplied to patients in the hospital or clinic ultimately rests with the central pharmacy, making it critical for pharmacy management to perform due diligence when selecting a W/D. Developing an approved distributor program and using an audit tool with targeted temperature controlled packaging focal points can assist in selecting and maintaining a distributor with validated or strategically monitored temperature control packaging to maintain drug efficacy.

#### REGULATORY BREAK

A break in cold chain management seems to occur between the federal and state audit systems. FDA's current Good Manufacturing Practice (cGMP) regulation, which is actively followed by drug manufacturers through distribution of finished pharmaceuticals, clearly addresses 'Holding and Distribution' in 21 CFR 211.142. It requires "Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected."<sup>1</sup>

Using stability guidelines, testing, and documentation, the manufacturer labels and distributes each product in validated packaging, monitored packages, or temperature control vehicles, and FDA checks for compliance in New Drug Applications (NDAs) and during regular on-site inspections. Stability test results are frequently used by the manufacturer to support shipping their products outside the label claim temperature (known as temperature excursions) for a limited and substantiated time. (Subsequently, however, the W/D transporting pharmaceuticals for multiple manufacturers to end users or to another W/D must maintain each drug product's label temperature, unless specifically authorized by the manufacturer for each drug on a formula basis.) No federal system updates the availability of stability exceptions for distributors and logistically it is safer to maintain all label temperatures from the

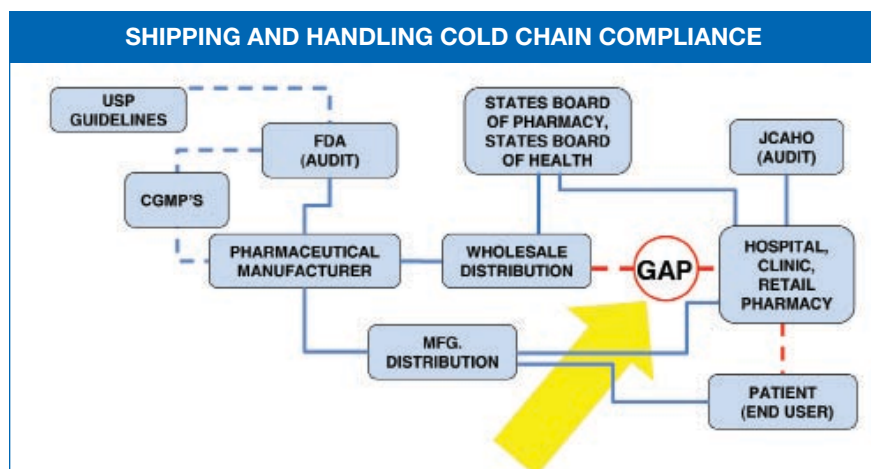


Figure 1. Inconsistent packouts that can be expected to freeze product create product safety concerns through the last mile of distribution.

W/D to the end user.

However, industry guidelines, developed by expert committees, heavily influence FDA and regulations. For example, the United States Pharmacopeia (USP), an independent organization, develops compendia definitions and guidelines. USP General Chapter <1079> Good Storage and Shipping Practices sets a

quality guideline for prescription and nonprescription drugs regarding storage, distribution, and shipping to properly maintain product stability. Developed to maintain the prescription's identity, strength, quality, and product purity, USP 1079 typifies FDA cGMPs in identifying the desired outcomes for drug transport without dictating the method.

As mentioned earlier, this study's gap analysis found that the hospital pharmacy's wholesaler/distributor lacked appropriate temperature control in their practices and packaging: Frozen gels were in direct contact with product cartons, and then mixed packout designs were observed after the observation was shared with the distributor. Several mandates

## TAILORING PACKAGING SYSTEMS TO COLD CHAIN CHANNELS

*PDA's Tech Report 46 prescribes the use of qualified packaging for product delivery to the end-user.*

By David Vaczek, Senior Editor

As the supply chain for controlled-temperature medicinals addresses the challenges of 'last mile' distribution, suppliers of thermal packaging have focused product development and services to this sector.

The Parenteral Drug Association has released Technical Report 46. Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User. The guidance covers proper handling and storage of temperature-susceptible product after it is handed-off by the manufacturer.

Tech Report 46 characterizes a complex system that involves multiple hand offs and multiple points in the supply chain where excursions outside the label long-term storage temperatures can occur.

"The manufacturer distributes in a well-controlled shipping lane that is routinely monitored for temperature excursions and is subject to uniform, stringent Good Distribution Practices. Conversely, shipping/



Cold Chain Technologies' KoolTemp GreenSmart pre-qualified and custom-designed EPS molded containers are available in a range of dimensions and internal volumes to support shipping in last mile channels.

distribution regulations vary widely from location to location, and uniform guidelines are lacking. This divergence has proven challenging for the pharmaceutical industry," the guidance says.

In the wholesaler distribution leg, 21 CFR, in defining wholesalers, "does not address packaging and shipping requirements for temperature-controlled products." And states' guidance on refrigerated drugs is vague or lacking, the guidance says.

"Without specific requirements, wholesaler distributors have no way of knowing if they are providing adequate, appropriate, and proper packaging and shipping temperature ranges (for maintaining products' integrity).

"In the absence of specific packaging requirements or stabil-

ity data provided by the manufacturer, the distributor should use qualified packaging or transportation to maintain product storage labeling requirements . . . from removal (from) the distributor's temperature-controlled environment until delivery at their customer's location," the report says.

Other areas covered include home delivery from mail service pharmacy, where business-to-business quality agreements should ensure suitable containers, temperature monitoring, and logistics.

Sharing of information within the supply chain will support pharmacists and nurses in educating patients on proper product storage. Dispensing personnel should become highly familiar with transport and storage requirements for vaccines, a particular distribution challenge due to their sensitivity to temperature, the report says.

### LOOKING TO EXCEL

"There is a tremendous upside potential to do a better job. There are many channels of distribution in the last mile out there, and we have to focus on and look at each," says Larry Gordon, president, Cold Chain Technologies (CCT; Holliston, MA).

"Specialty distributors and wholesalers want to excel in demonstrating best practices. This gives them the ability to distinguish themselves among their peers, and establish for the manufacturers they are using qualified systems," Gordon says.

The development of new drugs requiring temperature maintenance, and regulatory guidance covering cold chain practice



H-Series thermal control panels from Cryopak incorporate a handle for easy insertion and removal. Panels are offered for refrigerated (Phase 5) and room temperature (Phase 22) applications.

appear to direct the warehouse temperature control packouts; however the clout of an auditor knowledgeable in the nuances of cold chain appear to be lacking. For example, as early as 1987, the Prescription Drug Marketing Act required licensed wholesaler/distributors of prescription drugs to document detailed storage and handling procedures and employee train-

ing programs that address temperature and humidity control.<sup>2</sup>

In addition, as mandated by FDA, state licensing laws require adequate storage and quarantine areas within the W/D facility.<sup>3</sup> Additionally, Technical Report No. 39, revised in 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the

Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment, by the Parenteral Drug Association, provides further guidance on essential principles and practices to transport temperature-sensitive medicinal products through the supply chain.<sup>4</sup> Yet with all this in place, the refrigerated products are still being exposed to freez-



Cryopak's reusable Flexible Ice Pouch features a self adhesive strip for pouch flap sealing. An interior paper film material absorbs condensation.

are driving customer initiatives, says Bill Hingle, marketing director, TCP Reliable/Cryopak (Edison, NJ). "The pharmaceutical manufacturers have to maintain responsibility for the efficacy of the drug all the way through to delivery to the patient, demonstrating complete traceability. The only way for manufacturers to address this is to start viewing themselves as partners with their service providers, and develop networks to manage the accountability," Hingle says.

Gordon notes that manufacturers and distributors have differing needs operationally. "Manufacturers are generally working with more knowledge on the stability data, and will typically ship distributors in large packaging quantities. At the distributor level, the mix of products, quantity shipped per package, and order frequency differ.

"Their needs, while domestic, cover every corner of the country. In order to ship cost effectively, distributors look to us to use qualified packaging that can be tailored to support their lane and season-specific requirements," Gordon says.

CCT collaborates with distributors in the areas of maintenance of storage temperatures, definition of shipping lane profiles,

and pack-out development.

"They want data-driven qualified packaging with supporting documentation that is easy to use, cost-effective, and environmentally smart," he says.

"We are finding that distributors and 3pls are looking more and more for reusable temperature packaging solutions, as they look to meet the regulatory requirements for temperature sensitive products. Packaging has to be extremely cost-effective, while demonstrating maintenance of the product within label temperature range," Hingle says.

#### PATIENT HANDOFFS

Suppliers have developed packaging systems for farther down the chain, where product integrity assurance is required after delivery from the community pharmacy or mail order provider to the patient.

A new series of introductions in CCT's



The Flexible Ice Blanket from Cryopak can be cut to size as needed by the customer. Liquid-filled cells contain a patented thermal protection formula with a 5 degrees C phase point.

KoolTemp GreenSmart line will support community pharmacy distribution and mail order fulfillment. The home infusion market, where product is shipped directly from special distribution pharmacies to the patient's home, is another channel for which the cold chain will require qualified solutions, says Gordon.

"The cold chain presents different types and levels of handoffs. Our business model provides an integrated network of solutions whether in the delivery by distributors to pharmacies or in single-use delivery to the patient, says Hingle

"Engineered phase change materials are well suited to these applications because they address indirect costs by reducing the size and weight of the packaging. Our challenge is to develop a variety of cost-effective packaging platforms that can be used by distributors, 3pls, community pharmacies, or in mail order fulfillment," Hingle adds.

TCP Reliable acquired a new business unit this year to market Alternative Technologie Pharma, Inc.'s cold chain compliance solutions in the US.

ATP's products include the ATP-Mirador web-hosted solution for continuous real time tracking of temperature controlled products and storage facilities. The system's hardware and technology has been scaled down to provide a more cost effective solution for hospitals, Hingle says.

"Pharmacies have to be able to document and monitor their equipment to ensure it is functioning within specified ranges. (Using ATP-Mirador), hospitals can avoid the infrastructure expense of maintaining a data base. The system can be set up with alarms for immediate notification for corrective action," Hingle says.

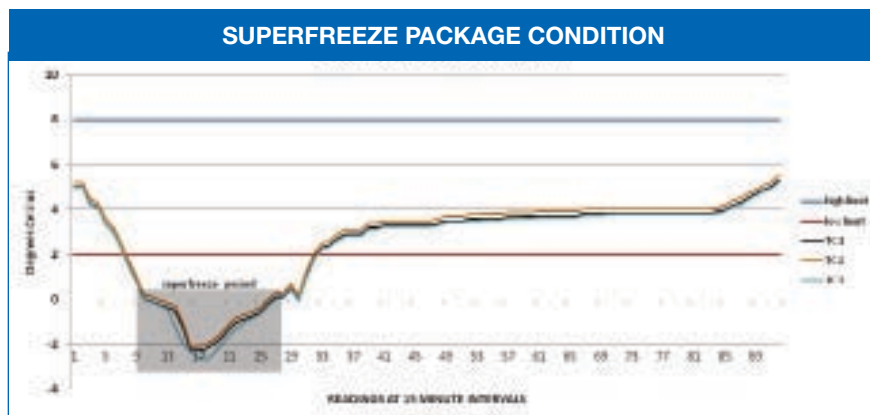


Figure 2. Gel packs pre-conditioned to minus 20 degrees C create an initial drop in product temperature to below 0 degrees, in manufacturers' packaging.

ing temperatures, regardless of risk.

Within the hospital, research suggests that individual State Boards of Pharmacy audit hospitals and retail pharmacies. An independent accreditation organization, The Joint Commission (JC), formerly known as Joint Commission on Accreditation of Healthcare Organizations (JCAHO) audits hospitals, medical centers, and clinics. (See Figure 1). However, most state governments utilize the JCAHO accreditation as a requirement of licensure. JCAHO audits its accredited medical facilities approximately every three years in unannounced visits to evaluate for suitability for reaccreditation. With the JC, Requirement for Improvement (RFI's) are issued for infractions. Corrections could be required immediately, but more typically within 45 days.

Nonetheless, these audits do not appear to be directed toward temperature control of pharmaceuticals incoming or during distribution within the hospital/clinic. Interestingly, an FDA compliance officer, Rosa Motta from the Center for Drug Evaluation and Research (CDER), shared in late 2008 that FDA would begin auditing the distribution environment, which is significant because it was being left to the individual State Boards of Pharmacy.<sup>5</sup>

## PACKAGE VALIDATION

Thermal Packaging Solutions (TPS) Ocean, NJ, a consulting group independent of suppliers, develops protective pharmaceutical packaging, temperature controlled packaging, seasonal weather

profiles, storage and packing line analysis, protocols/SOPs and has audited manufacturers/suppliers/contractors/distributors collectively for over 50 years. From our experience, temperature-controlled packaging for shipping temperature-sensitive pharmaceuticals to the end users most frequently includes various insulated containers including polystyrene, polyurethane, vacuum panels and aerogel and a phase change material (PCM; also called gels) to manipulate and maintain the temperature. PCMs or gel packs change temperature quickly from the preconditioned temperature to the phase change temperature, then more slowly as they phase from solid to liquid or vice versa (Note: Frozen products frequently ship with dry ice which sublimates from a solid to gas).

In the past 10 years, pharmaceutical manufacturers honed their thermal packaging validation work to represent environmental temperature and humidity considerations and in the past five years, FDA issued many 483s or Warning Letters (mandates from FDA for immediately or short-term corrective actions) directing that manufacturers control distribution temperatures to that which is supported by stability results. In NDAs, FDA reviews the manufacturer's on-site documentation and practices, observing for packout design (combination of container and gels at specified temperatures), which matches validation study results to safely ship product from the manufacturer's facility with temperature control. For

many manufacturers, validation studies qualified a separate design for winter versus summer to avoid additional buffer gels and reduce the shipping weights. Alternatively, manufacturers have inserted temperature monitors in shipments in sufficient quantity and spacing to prove temperatures were maintained throughout the load.

For the drug manufacturer, the shipping temperature range can vary from the label temperature provided stability testing supports the temperature excursions for the shipping time (e.g., label temperature 2 to 8°C. Manufacturer stability backed shipping temperature 1 to 15°C for maximum of 24 hours). In the case of biologics, it is unusual to have stability testing support any freezing of the products.

In post validation testing, drug manufacturers purchase specified materials, precondition gels to prequalified temperature limits, and pack product to exactly match the validated designs following standard operating procedures (SOPs). Records of training are mandatory.

Historically, manufacturer's refrigerated product packouts almost exclusively packed insulated containers with gels preconditioned to -20°C, the temperature of off-the-shelf freezers. An initial drop in product temperature to below 0°C was deemed unavoidable and accepted despite a lack of stability data at this temperature, and the prospect in some cases of degradation. Validation studies found it difficult to impossible to maintain temperatures above freezing without buffering products with added refrigerated or in some cases room temperature gels or other barrier, making containers significantly heavier and more costly to ship. As expected, product nearest the -20°C gel froze first and most deeply. Stability studies didn't support the practice, but the habit became accepted as an initial "Super Freeze" in the industry. Recently, TPS successfully challenged many manufacturers to reprogram the preconditioning freezer to approximately -5°C and deliver a PCM temperature closer to the desired product label temperature, but still maintain distribution temperatures,

thereby validating packout designs without Super Freeze. (See Figure 2.)

## HOSPITAL GAP ANALYSIS

Despite significant progress and mandated temperature control of pharmaceutical distribution from the manufacturer, recent observations at several of the industry's largest U.S. pharmaceutical distributors noted the use of approximately  $-20^{\circ}\text{C}$  gels often in direct contact with refrigerated product (labeled storage temperature 2 to  $8^{\circ}\text{C}$ ). Also noted were the actual packout designs that varied in gel quantity and positioning within thermal containers (totes or manufacturers' reused thermal containers.) As mentioned earlier, the W/Ds are normally not privy to the stability test results for each product that are contained in the NDA and updated each subsequent year of stability testing. It is only by contacting manufacturers, product by product, and package size by package size, that time versus temperature information could be gathered then used to ship outside of the labeled temperature. This is an extremely unlikely situation.

To further capture and evaluate the state of temperature control of pharmaceuticals as received from distributors, TPS and Brigham and Women's Hospital, (a world-renown leader in patient treatments, technologies, quality and safety), teamed up for a case study. This hospital receives pharmaceutical shipments directly from a local top-three distributor several times a week with the largest shipments being received on Mondays. A representative shipment, which included several pallets stacked primarily with locked reusable plastic totes, was inspected. Refrigerated product containers were identified by label color, pulled aside, inspected, and found to be either of two types of insulated containers with frozen solid gels:

- Small hard plastic reusable tote lined with  $\frac{1}{2}$  to  $\frac{3}{4}$  in. thick molded expanded polystyrene (EPS) case (two pieces). Product cartons found in direct contact with single frozen solid gel pack  $\sim 1$  lb. No bubblewrap or other divider

separated the frozen product and gel. No temperature indicating monitor or indicator included.

- Medium size molded two piece EPS  $\sim 1\frac{1}{2}$  in. thick cooler. Single larger  $\sim 2$  lb frozen gel laid directly on top of product cartons without separator/divider, or sets of 3 gels  $\frac{1}{2}$ -in. each in thin plastic bag stacked to one side but in direct contact with product cartons inside. No temperature monitor or indicator included in shipment.

In both cases, with frozen gels in direct contact with the product cartons, the packouts can be expected to deliver sub-zero assaults and frozen product temperatures, possibly throughout the packout, but certainly near the gel packs. Even if the frozen gel precondition temperature had been altered to  $-10^{\circ}\text{C}$ , products slightly separated from the gels with  $\frac{1}{2}$ " or 1 in. of bubblewrap have been found to freeze the nearby products in validation studies. And as cited earlier, typical gel preconditioning freezer temperatures at distributors were found to be approximately  $-20^{\circ}\text{C}$ , the typical unaltered stand alone freezer temperature. (See Figure 3.)

## DISTRIBUTOR AUDIT

In this study, after hospital discussions regarding the packouts and concern for maintaining label temperatures, the W/D indicated that bubblewrap separators should have been included in the shipments. Packers would be retrained immediately. Additionally, this hospital introduced their intent to audit the W/D and review a newly developed audit questionnaire. Disappointingly, review of a refrigerated products shipment several weeks later found marginal improvement and further concern over inconsistency in the packouts. There were some gels in bubblewrap, and some not and in direct contact with product. One packout had no carton providing an additional spacer.

The hospital requested an audit at the W/D's packaging site, using a Hospital Distributor Audit Questionnaire developed by Thermal Packaging Solutions. The questionnaire—recommended for any distributor audit—requests informa-

tion in multiple areas, including operations performed at the site, control, warehousing, and inventory of salable goods, customer order handling, package qualification, and temperature management.

## CONCLUSION

The studies documented a break in the cold chain from the wholesaler/distributor to the hospital. It identified a high degree of potential deleterious distribution of refrigerated pharmaceutical products in thermal packaging that can be expected to reduce if not obliterate the efficacy of some pharmaceutical products like the biologics, which are sensitive to freezing and expected to grow in volume. The analysis documented the results of a suspected lack of regulatory control over local pharmaceutical distributors, which are not owned/operated by a pharmaceutical manufacturer, in the areas of training, validation of packaging and very likely SOP's. A safety gap from wholesaler/distributor through the "Last Mile" to the patient.

Audits by a reviewer knowledgeable in the area of cold chain, preferably by the end user or their representative, and with an accompanying audit tool which directs the review through temperature control in packaging designs, validation, packouts, SOP's and training, needs to be implemented as part of an ongoing hospital/ medical center/out-patient pharmacy supplier program to direct hospital, clinical and retail pharmacies toward quality suppliers delivering pharmaceuticals with the designated efficacy.

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