DANGEROUS GOODS
A DIVISION OF BERLIN PACKAGING

berlin™ PACKAGING

SHIPPING TEMPERATURE-SENSITIVE MATERIALS

Considerations in Packaging Selection

EXECUTIVE SUMMARY

One of the biggest risks in shipping temperature-sensitive products such as vaccines, pharmaceuticals, medical devices, biological products, and certain chemicals throughout the cold chain (supply chain) is potential product loss or adulteration due to temperature excursions or package damage. According to the World Health Organization, over half of all vaccines worldwide are destroyed because of freeze-damage. This paper offers guidance to those new to the cold chain for selecting the right packaging solutions for products requiring thermal protection.

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INTRODUCTION

Lives are dependent upon the safe and secure transport of vaccines and pharmaceuticals as well as biological substances such as plasma, blood, organs, vaccines, and tissue. The market for these types of products is in the trillions world-wide. The overall economic impact of the biopharmaceutical sector alone on the U.S. economy, as measured by a 2011 Battelle Report,[1] totals more than $917 billion on an annual basis, comprised of $382 billion in direct impact by biopharmaceutical businesses, and $535 in indirect and induced impact on the overall economy.

With lives on the line, and billion-dollar markets depending on a viable supply chain, risk mitigation is critical. Two of the greatest risks in the supply chains of temperature-sensitive products are adulteration due to damage or temperature excursions (deviation from required ranges), and non-compliance with applicable laws and regulations. The costs for temperature excursions are high. Another study[2] found that by cutting shipping excursions and site temperature deviations in half, a small company with 150 clinical trials worldwide could save over $2.0M and free up at least eight people to perform other work.

Both of these risks can be mitigated with the right supply-chain expertise. In this paper, we focus on understanding the cold chain and temperature controlled packaging. We will address:

- Cold chain basics
- Temperature controlled packaging basics
- Packaging selection: materials
- Packaging selection: variables
- Useful resources

Before discussing packaging, we will begin with the basics of a cold chain.

COLD CHAIN BASICS

The "cold chain" is a logistics network designed to maintain optimal conditions during the packaging, handling, labeling, shipping and storage of perishable items. The goal is to ensure that the perishable products are ready for use when reaching their end-user. This means that the cold chain system must maintain a temperature specific to the products being shipped.

Temperature excursions cannot be tolerated. But, transit risks can be great. Tarmac temperatures can climb quickly during staging and loading, yet at a typical cruising altitude for an aircraft, temperatures can plummet to -20° C. Natural disasters, poor weather, or human-caused events, such as delays at customs, could also interrupt the planned transport route and unexpectedly increase time in transit.

A successful cold chain requires the support of highly trained personnel, the proper packaging, the proper transport and storage equipment, as well as efficient management procedures. Our focus next turns to the basics of the packaging used to control product temperature.

[1] "The U.S. Biopharmaceuticals Sector: Economic Contribution to the Nation," Battelle Technology Partnership Practice Report, July 2011.

[2] "Modeling the Clinical Trial, Calculating Company-Wide Savings and Comparisons Among Several Alternative Distribution Ideas," *Pharmaceutical Outsourcing Journal,* May/June 2012.

TEMPERATURE CONTROLLED PACKAGING BASICS

Temperature controlled packaging (TCP) is one element of the cold chain. TCP is designed and validated to rigorous standards to keep products within a specific temperature range for a given time period. Many pharmaceuticals, for example, need to stay between 2° C and 8° C. Other materials may need to maintain a frozen temperature or a controlled room temperature state, such as 25° C.

There are three types of TCP solutions: active, passive, and hybrid systems. Active systems include refrigerated boxes and pallet shippers, which may operate via a power source, like a lithium battery. Passive systems rely on insulated packaging along with a refrigerant, such as wet or dry ice, gel packs or wraps, foam bricks, phase change materials (PCM), or liquid nitrogen. Finally, hybrid TCP systems incorporate elements from both active and passive TCP solutions.

Passive systems are practical, cost-effective, and can be designed to suit many situations. We will focus the remainder of this paper on passive solutions. A common passive TCP shipper consists of:

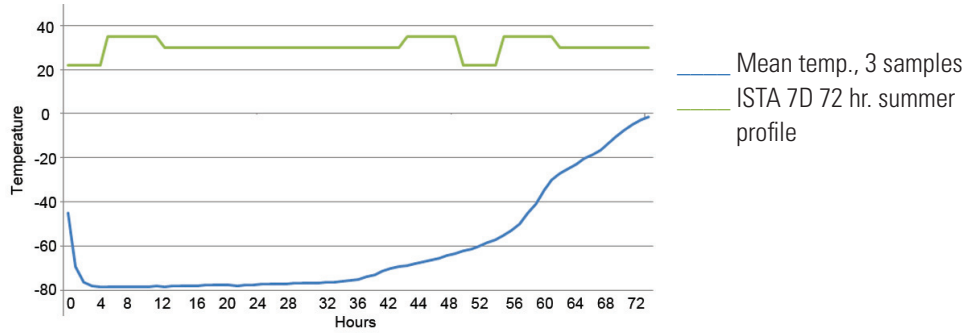
- An outer corrugated carton
- An inner cooler
- Refrigerant
- Primary containers such as specimen bags or vials
- Protective packaging (such as peanuts or "dunnage" to fill void spaces)
- Leak-proof bag and absorbent (for air transport of Category A and B biological substances)
- A temperature data logger may also be used

The system is so elaborate to ensure the temperature parameters are met. Indeed, for many pharmaceutical, medical, biotechnology, and (hazardous) chemicals, the packaging system must be tested and proven to meet performance standards required by various regulatory bodies. These include the U.S. Food and Drug Administration (FDA), U.S. Department of Transportation (DOT), and the International Air Transport Association (IATA). Though IATA is not a regulatory body, the majority of the world's air carriers specify the rules under which they will transport hazardous materials in IATA's Dangerous Goods Regulations (DGR).

Some of the standard tests performed by certified testing laboratories to validate the packaging system's durability and/or ability to maintain temperature include the International Safe Transit Association (ISTA) standards 3A, 20, 7D, and 7E; and ASTM International (ASTM) standard D3103.

For example, ISTA has written the 7D profile to include both summer and winter conditions, since hot extremes and cold extremes can vary depending on time of year. The profiles specify durations of specific temperature ranges used to test the packaging system. The profile is then programmed into a special thermal chamber designed to test the package. On the next page is a graph showing the results for an ISTA 7D summer profile test, showing that the given packaging (in this case an EPS foam thermal shipper) will stay frozen (under 0° C) for up to 72 hours. The green line above is the programmed

temperature profile used within the thermal chamber, which shows the temperature variations per unit of time within the chamber. The blue line below it is the mean temperature of three sample packaging systems tested within this chamber.



TCP can also be subjected to the rigorous test procedures specified in Title 49 of the CFR. This ensures hazardous temperature-sensitive materials such as aerospace adhesives (flammable liquids/solids), infectious substances, and radio-pharmaceuticals (radioactive) can meet the performance test requirements for the transport of dangerous goods. The 49 CFR tests subject the pacakging system to shock, drop, vibration, water absorption, and pressure in order to achieve a United Nations (UN) rating. Going into the details here are beyond the scope of this paper, but the Useful Resources section of this paper provides suggestions for learning more.

PACKAGING SELECTION: MATERIALS

When selecting a package and refrigerant to best maintain your product temperature and protect against physical damage during shipment, there are a number of different factors that must be considered. For example:

- What are the physical characteristics and payload of the material to be shipped?
- What temperature range needs to be maintained, and for how long?
- Do you plan to re-use the packaging? Can it be re-used? For how long?
- What transit conditions (rough, shocks, extreme temperatures) do you expect?
- What season(s) do you expect to ship in?
- What temperature ranges will the shipment be exposed to during transit?
- What regulations impact packaging selection?
- What is the total cost you're willing to absorb?

A good place to start evaluating your options is to review the characteristics of the insulating material and refrigerants, comparing their relative merits against the needs you identified by answering the questions above.

INSULATING MATERIALS. The three most common types of insulated packaging for non-bulk shipments of temperature-sensitive materials include EPS foam, polyurethane foam, and vacuum insulated panels (VIP). The relative merits of each type are detailed in the table on the following page.

	Insulating Materials		
	EPS Foam	Polyurethane Foam	Vacuum Insulated Panels (VIPs)
Benefits	• Lightweight • Inexpensive • Recyclable • Re-usable	• Good shock absorption from drops or hits • Superior crush/ compression protection • Re-usable many times	• Lowers freight and shipping costs • Requires less refrigerant • Greater net payload • Recyclable • Re-usable many times • Protects product from water molecule intrusions
R-Value*	Lowest	Medium	Highest
Best Suited For	• Delivery and storage of refrigerated or frozen materials	• Highly temperature-sensitive shipments • Heavy payloads	• Highly temperature-sensitive payloads • High-value shipments • Extended shipping windows • International shipments
Optimal Transit Duration	≤ 24 hrs.- ≤ 48 hrs.	> 48 hrs.	24 to 96+ hrs.

* The capacity of an insulating material to resist heat flow. The higher the R-value, the greater the insulating power.

In addition to the insulating materials detailed in the table above, the cold chain supply marketplace offers a myriad of other options you may wish to explore, including thermal blankets, insulating (soft-sided) pouches, hard-cased thermal chests, and cryogenic units.

REFRIGERANTS. The more common refrigerants are listed below as well as some of the relative merits of each type. Keep in mind that refrigerants and insulating packaging must be considered as a complete system.

Dry Ice

- Special handling and training is required for use (See the 49 CFR).
- Regulated as a hazardous material/dangerous good in air transport.
- Locating a local supplier is necessary.

- Not for use if product is adulterated by extreme cold.
- As it sublimates, void spaces will open and the product may shift in transit.

Gel Packs

- Available soft or rigid, in a variety of shapes, sizes, and thicknesses.
- Will maintain shape as they thaw.
- Non-rigid gel packs may not maintain shape as they freeze.
- Can be re-washed, re-conditioned, and then re-used.

Gel Mats

- Provide cushioning for fragile shipments.
- Stays frozen longer than wet ice (without moisture leakage).

Foam Bricks

- Semi-rigid; they don't lose shape as they thaw, nor when they freeze.

Phase Change Materials (PCM)

- Protect against temperature excursions for an extended window.
- Provides tighter temperature control than other options.
- Enables temperature control outside of frozen or refrigerated ranges, i.e. controlled room temperature.
- Reduces shipping weight and freight costs, as less is often needed.
- Simplifies pack-outs.
- Can be re-washed, re-conditioned, and then re-used.

By considering the refrigerants and insulating materials together, the shipper can then begin to evaluate specific shipping systems. For example, if the product to be shipped is highly temperature-sensitive and needs to withstand international travel conditions (and potential delays), the shipper might select phase change material as the refrigerant, a cooler with a higher R-value (such as polyurethane or VIP), and strong protective packaging, to evaluate for suitability. Third party labs and logistics partners, as well as packaging partners, can assist in qualifying and validating packaging to ensure it performs as intended.

PACKAGING SELECTION: VARIABLES

There are other factors to consider when evaluating the potential packaging solution. These factors should be weighted according to your internal goals, limitations, and needs.

Freight Optimization

- **Consider the R-value.** Packaging with a lower R-value may require more refrigerant to maintain the ideal temperature, increasing total freight costs.
- **Consider packaging costs vs. freight costs.** EPS foam shippers with dry ice or gel packs are less expensive than polyurethane or VIP systems, but the total weight of the EPS solution considered over all of your shipments may make those other options attractive.

- **Payload maximization.** The higher the R-value, the less packaging and refrigerant required, thus shrinking the size and weight of the package and maximizing payload.

System Cost

- **Custom packaging solutions vs. "off the shelf" solutions.** Custom packaging tailored to your specific payload can significantly reduce component costs as well as cut down shipping and freight costs.
- **Consider re-usable systems.** They can be more environmentally-friendly, reducing overall carbon footprint in transit; and significantly reducing packaging cost-per-turn.
- **Consider packaging costs vs. product replacement costs.** If you're shipping high-value material that cannot tolerate temperature excursions, consider the highest R-value packaging for peace of mind and reduced product loss or cost of replacement.

Pack-Out Simplicity

- **Simple pack-outs reduce errors** in preparing sensitive specimens and other products for shipment. They ensure the package is closed properly every time, meaning your product arrives safely and at the proper temperature. Additionally, smaller end-users might not have access to the equipment needed to condition gel packs or other materials if needed, or to store the material within the proper temperature window for a length of time.
- **Consider potential hazards in your pack-outs.** Active shippers may use lithium batteries, and hybrid shippers may require dry ice, a hazardous material (also regulated in air transport). Custom phase change materials may pose toxicity or transport restrictions. Use of these materials may require enacting a safety plan.
- **Package weight and size impact pack-outs.** Consider these early on when designing or selecting packaging. Dry ice, gel packs, and PCM all have certain benefits but certain limitations, as discussed earlier.

Thermal Performance

- **Consider the R-value of the packaging.** EPS foam has the lowest R-value, so it won't provide protection over very long periods. Its construction may not be as consistent as other materials, further risking temperature excursions. Polyurethane and VIP shippers offer more consistent and longer thermal protection.

Physical Performance

- **The stability and durability of the packaging matters.** Heavy payloads are more suited to polyurethane coolers. Return and reuse (reverse logistics) programs put significant stress on the cooler, making polyurethane and VIP coolers more practical than EPS foam in most situations.
- **Ensure your packaging is validated to the proper standard.** As discussed, regulatory bodies including the U.S. DOT and U.S. FDA, as well as other organizations, may specify that packaging meets certain performance standards. Be aware of what they require and test your packaging systems.

SPOTLIGHT ON THE DANGEROUS GOODS DIVISION

Berlin Packaging is a leading supplier of rigid packaging, and its Dangerous Goods division specializes in shipping systems for the safe transport of hazardous materials as well as temperature-sensitive products. For over 30 years, the Dangerous Goods team has been designing and assembling UN-certified and temperature-sensitive packaging in a wide variety of styles.

The division offers a selection of over 1,600 stock packaging systems as well as the ability to custom-design solutions to meet a customer's exact needs. In addition to in-house UN and thermal testing capabilities, the division uses a third-party lab to independently certify each UN rated packaging system, and upon request will use a third-party to validate thermal packaging.

Berlin Packaging's Dangerous Goods division is ISO 9001:2008 certified and has a dedicated sales force and packaging engineers with expert knowledge of the regulations and requirements related to shipping hazardous and temperature-sensitive materials.

USEFUL RESOURCES

There are many guidance documents within the regulatory sphere and from industry considered to be best practice for handling, storage, transport and distribution of temperature-sensitive materials. A few are listed below.

- 21 CFR, Food, Drug & Cosmetic Act, Chapter V: Drugs and Devices
- 49 CFR, Hazardous Materials, Chapter I: Other Regulations Relating to Transportation
- European Medicines Agency (EMA)
- IATA Perishable Cargo Regulations, Chapter 17
- U.S. Pharmacopeial Convention (USP) Chapter 1079, Good Storage and Shipping Practices
- EU Pharmaceutical Legislation for Medicinal Products for Human Use, Vol. 1
- EU Pharmaceutical Legislation for Medicinal Products for Veterinary Use, Vol. 5
- The World Health Organization (WHO) Model Requirements for the Storage and Transport of Time and Temperature Sensitive Pharmaceutical Products
- Parenteral Drug Association (PDA) Technical Report No. 39, Guidance for Temperature-Controlled Medicinal Products
- PDA Technical Report No. 52, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User

GETTING STARTED

A successful cold chain requires the support of highly trained personnel, the proper packaging, the proper transport and storage equipment, as well as efficient management procedures. This paper presented several insulating material and refrigerant options as well as some of the benefits and trade-offs of each.

Reviewing the questions asked earlier in this paper will help focus an evaluation of the options presented:

- What are the physical characteristics and payload of the material to be shipped?
- What temperature range needs to be maintained, and for how long?
- Do you plan to re-use the packaging? Can it be re-used? For how long?
- What transit conditions (rough, shocks, extreme temperatures) do you expect?
- What season(s) do you expect to ship in?
- What temperature ranges will the shipment be exposed to during transit?
- What regulations impact packaging selection?
- What is the total cost you're willing to absorb?

Use the answers to review the information presented in the packaging selection materials and variables to guide the selection process. Consulting experts in any of these steps is a prudent way to move quickly through the process while minimizing risk.

SUMMARY

The economic and human value of products shipped throughout the cold chain is enormous, and transit, as well as regulatory, risks can be great. Packaging plays an important role in avoiding expensive, and sometimes catastrophic, loss of product due to temperature excursions and or damage to the packaging system. By systematically evaluating the products to be shipped, the cold chain from start to finish, and choice of packaging supplier you'll lower your risk exposure. We reviewed several variables that need to be considered in selecting the right packaging solution. Partners exist to help each step of the way. Companies of all sizes and sophistication often look to these experts to create, supply, and manage their packaging inventory.

ABOUT BERLIN PACKAGING

Berlin Packaging is North America's premier Hybrid Packaging Supplier of plastic, glass and metal containers and closures. With over 33,000 available SKUs, over 120 packaging consultants, and more than 90 sales and warehouse locations across North America, the company has the right products, expertise, and geographic proximity to help customers increase their net income through packaging products and services. Berlin Packaging supplies billions of containers and closures annually as well as warehousing and logistics services for customers of all sizes in all industries. It is the only company in its sector to be ISO 9001 certified, to have Customs-Trade Partnership Against Terrorism (C-TPAT) certification, and to achieve 99% on-time delivery of its shipments every month for over eight years. Related services include Studio One Eleven, a full-service custom packaging and graphic design division; Berlin Global Packaging Group, a global sourcing solutions provider including custom packaging, order and quality management, and logistics; E3, a consulting division that helps customers unlock profit; Berlin Financial Services, which provides financing for equipment and capital improvements; Dangerous Goods, offering safe, economical, UN-certified packaging solutions for shipping dangerous and temperature-sensitive goods; Freund Container & Supply, a need-it-now packaging and industrial supplies provider with no minimum order requirements; and Qorpak, a global supplier of laboratory packaging and supplies. The company can be reached at 1-800-2-BERLIN, BerlinPackaging.com, and on LinkedIn and Twitter.