Choosing the Right Passive Thermal Packaging Solution

An Evaluation Guide for Life Science Organizations
Introduction
The expansive growth and regulation of temperature sensitive distribution has led to an overwhelming number of thermal packaging options available on the market today. This whitepaper provides life science organizations an all-encompassing tool, regardless of the market or distribution segment, for evaluating temperature sensitive packaging across seven critical categories identified from market surveys including best practices for specific market segments.

Background
The growth that is occurring in temperature sensitive distribution, especially with biologics, has been well documented and is expected to continue at an annual compound growth rate of more than 9.5%.¹ In 2013, seven of the top eight and eleven out of the top twenty-five bestselling drugs were biologic-based including the three largest². Biologic agents are expected to represent 19-20% of the total market spending, or $221Bn, in 2017.³ Sales of generic biologics, or bio-similars, are expected to increase from less than 0.5% in 2012 to 2-5% in 2017³. Additionally half of the 900+ biologic or specialty therapies currently in clinical trials will need to maintain a specific temperature range to work effectively⁴ upon commercialization. Increasing
global regulations have led to greater scrutiny of the supply chain process including packaging, temperature monitoring, and logistics services. Bio-similars will see major acceleration as many large molecule therapies lose patent protection. Expanding and complex global regulations complicate the business further leading to higher distribution costs. Properly protecting products at the lowest total cost has become imperative to maintain or grow market share in the competitive global marketplace.

THE BIOLOGICS MARKET

<table>
<thead>
<tr>
<th>Year</th>
<th>Biologic share of total sales</th>
<th>Global Biologics Size</th>
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<tr>
<td>2002</td>
<td>11%</td>
<td>$46Bn</td>
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<tr>
<td>2007</td>
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<td>$106Bn</td>
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<td>18%</td>
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<tr>
<td>2017</td>
<td>19-20%</td>
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Biosimilars share of biologics:

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<th>Year</th>
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<td>2007</td>
<td>0.5%</td>
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<tr>
<td>2012</td>
<td>1.0%</td>
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<td>2017</td>
<td>2-5%</td>
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Source: IMS Health Thought Leadership, September 2013
1. Thermal Performance

Designing custom thermal packaging is a delicate balance of taking many different factors into consideration.

Overdesigning packaging to withstand 100% of any possible weather event on Earth results in large, heavy, and expensive systems. Underdesigning with low component costs as the primary goal runs the risk of experiencing failures in the field.

These failures, when detected through the use of temperature monitoring devices, are extremely costly. Undetected failures can pose significant risk to patient safety and public health.

The best method of comparing thermal packaging is to perform side-by-side testing in environmental chambers. The best method of comparing thermal packaging is to perform side-by-side testing in environmental chambers. Identical ambient temperature profiles, payloads, and thermocouple wiring should all be used to control performance differences solely attributed to system design. Resources often prohibit end users from conducting this level of testing.

There are three key ways to evaluate the thermal performance of competing systems that were initially tested to different criteria. Each packaging supplier should provide their own testing documentation for review.

These three variables (ambient temperature profiles, payloads, and thermocouple wiring) can be evaluated as follows:

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THERMAL PACKAGING EVALUATION CRITERIA*

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*Based on the results of the “Thermal Packaging Scorecard” conducted by Cold Chain Technologies.
**Ambient Temperature Profiles**

Ambient temperature profiles are used to mimic expected high and low temperature shipping environments. These profiles are programmed into laboratory thermal testing chambers, while packages are subjected to anticipated conditions, and system performance is evaluated.

Cold Chain Technologies, Inc. (CCT) has characterized and cataloged hundreds of ambient temperature profiles and uses advanced tools to evaluate them across several different criteria.

Two simple calculations used to get a baseline comparison are Total Energy and Mean Temperature.

**Total Energy:**

Total Energy is the sum of all time and temperature points of the profile, which is often referred to as the “area under the curve.”

Sum all of the temperatures at each time point to come up with a °C*hr. value.

Generally, higher numbers are more severe for summer testing and lower numbers are more severe for winter testing.

Figures 1 and 2 show two different ambient temperature profiles and their associated total energy.

**Figure 1** has higher temperature spikes, and may at first seem more severe, but it is actually **Figure 2** that shows a profile with higher cumulative heat throughout the summer cycle.

**Mean Temperature:**

Mean temperature is the Total Energy divided by the Profile Duration. Profiles with mean temperatures closer to the desired payload temperature result in less robust packaging while those farthest from the desired payload temperature generally result in more robust packaging.

\[
\text{Mean Temperature} = \frac{\text{Total Energy}}{\text{Profile Duration}}
\]
THERMOCOUPLE WIRING

Thermocouples are highly accurate temperature-measuring instruments placed into the shipping system during environmental chamber qualification. These instruments record temperature throughout the qualification process.

During the testing process, it is important to understand where thermocouples are placed. Your packaging supplier should be able to provide this information within testing protocols and reports.

For geometrically symmetric passive shipping systems, thermocouples are typically placed in the top corner, top center, bottom center, side center, and bottom corner – at a minimum.

Moreover, thermocouples should not only be at the geometric extremes of the payload tested, but the payload itself should be at the geometric extremes of the available payload volume. Only then is all of the marketed payload volume “covered” per the qualification documentation.

PAYLOADS

When packaging manufacturers perform internal testing, the selection of payloads for prequalified containers is entirely at their discretion. Payload characteristics can greatly influence the overall performance of a system (reference Figure 3).

Thermal mass is a basic comparison tool but a more comprehensive tool is Volumetric Heat Capacity (VHC) (reference Figure 4). VHC is the product of density and specific heat.

For many years it was common practice to consider a minimum payload as worst case but this is not necessarily correct. As the payload volume of a thermal shipping system is usually exposed to a non-uniform transient temperature distribution, there are scenarios where the max load is the worst case thermally. The worst case payload for thermal testing is the one with the lowest VHC while occupying the largest available product space within the system.

Figure 3

![The Amount of Liquid Payload Pre-Qualified Packages are Tested with Matte](image)

\[ VHC = \rho \cdot C_S = \left[ \frac{J}{m^3 \cdot K} \right] \]
2. System Cost

**Fully laden purchase price of all packaging materials**

The unit cost of packaging materials is only part of the total cost of ownership equation. Supply locations, truck, air or sea container loading efficiency, and method of transport will all impact incoming freight costs per unit.

The space saving benefits of knocked down (a.k.a. flat pack) materials must be weighed against any set up time, pack-out complexity, and thermal performance deficits when compared to set up systems (a.k.a. pre-assembled) that require more storage space.

3. Freight Optimization

Outgoing freight costs often outpace packaging costs 4:1 or more. Freight optimized packaging, even when designed at a premium cost, can be used to effectively reduce the total cost of goods distributed.

**Small Parcel Freight**

Small parcel freight rates are based on the higher of actual weight or dimensional weight (DIM). The most efficient system has an actual weight equal to dimensional weight.

Companies with a high volume of shipments have the ability to negotiate DIM factors, which are used to calculate DIM weight (Figure 5), that result in more advantageous shipping rates for larger packages.

**Bulk Freight**

The majority of life science bulk freight moves internationally via air. Similar to small parcel shipments, bulk freight is paid based on the higher of dimensional weight vs actual weight. When multiple pallets of product are sent in a single shipment to a single destination, then designing around the standard PAG and PMC air cargo pallets (a.k.a. “cookie sheets”) (Figure 6) can result in lower freight costs vs. systems that do not optimize fractional sections of the PAG and PMC air cargo pallet. Bulk freight optimization can be seen as designing from the “outside in”. This often, but not always, means the system is not payload or warehouse optimized.

4. Payload Optimization

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**How to Determine Dimensional Weight**

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<thead>
<tr>
<th>Dimensional Weight (lbs)</th>
<th>L x W x H</th>
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<tbody>
<tr>
<td>Domestic Shipments</td>
<td>166</td>
</tr>
<tr>
<td>International Shipments</td>
<td>139</td>
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</tbody>
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**Figure 5** Set by leading common carriers, 166 is the standard DIM factor for calculating domestic shipping costs while 139 is the standard DIM factor for international freight calculations.

**Figure 6** KoolTemp® GTS 1100 liter is a freight optimized one quarter PAG bulk shipping system.
A recent Georgia Tech University survey found that greater than 90% of temperature excursions were the result of human error, with the vast majority attributed to errors during pack-out.
Sometimes initially overlooked, but just as important as the testing criteria, is the pass or fail criteria. Often it is considered a “pass” if the secondary package, and it’s contents, are in saleable condition. This means the shipping systems and components can show damage as long as the contents to be sold are OK. It is critical that such pass or fail criteria be agreed upon up front and is specified when reviewing the “passing” performance of one system vs. another.

7. Environmental Impact

Reducing environmental impact continues to be of high importance to Cold Chain Technologies, Inc. and our clients. This is quantified in many different ways from the reduction of materials used during manufacture, to carbon footprint or life cycle analysis (LCA). Shipping systems can be made of recycled materials, recyclable materials, biodegradable materials, bio-based materials, compostable materials, or any number of “environmentally friendly” approaches.

Cold Chain Technologies, Inc. has invested in many environmentally conscious materials and practices from biodegradable single use systems to re-usable systems and refurbishment programs. In general, environmental impact and disposal considerations for direct to consumer shipments receive the most scrutiny for environmental impact. It is important to understand your company’s environmental sustainability goals when making a determination about your packaging’s impact on the environment.

Beyond internal sustainability goals it is often beneficial to seek input from sales and marketing teams who provide insight into your customer’s perceptions. Customer satisfaction goals, particularly important in specialty pharmacy to patient relationships, can be achieved through the use of environmentally friendly materials. Unfortunately there is an abundance of misleading product marketing, also known as “green washing”, with respect to insulated shipping components. When implemented properly a return re-use program achieves a multitude of environmental benefits and reduces total cost of ownership (TCO).
Clinical Trial Product Shipments

Clinical trial product shipments often involve high dollar or irreplaceable therapies. These investigational drugs are given to patients under strict protocol. In the event a shipment is lost due to thermal degradation or physical damage a patient may be unable to receive treatment as specified in the protocol and subject removal from the clinical trial study is possible. The cost to bring a drug to market is currently estimated at $5 billion* taking into account therapies that never reach commercialization. Jeopardizing a study can put enormous amounts of capital at risk and delay potentially life-saving treatments to thousands of individuals. Therapies at this stage of development are typically required to maintain strict temperature ranges such as 2°-8°C or 15°-25°C, without any excursion allowances, because stability studies have not yet been completed.

Greater than 90% of clinical trial shipments are fully monitored through the use of data loggers. Pack-out simplicity is critical because any error during pack-out could put thermal performance at risk. The cost of failure for clinical trial shipments is extremely high. High performing and robustly tested shipping solutions are a necessary part of operating with high assurance levels.

Best practices to follow:

1) Utilize pre-qualified shipping solutions with universal pack-outs. Universal pack-outs allow the same refrigerant configuration and conditioning to be utilized year round regardless of the origin, destination, or time of year. This provides the highest level of thermal protection, particularly if shipments are made from hot to cold or cold to hot climates and when shipments are made during “shoulder seasons” (spring & fall).

2) Select pre-qualified shipping solutions that are tested against robust ambient temperature profiles such as the “18/6” summer and winter profiles utilized by Cold Chain Technologies, Inc. (CCT) and other leading packaging suppliers. ISTA profiles have also been utilized with success. Avoid systems tested against ambient profiles with rapidly oscillating temperatures above and below your product criteria.

3) Avoid systems that require secondary conditioning of refrigerants for optimal performance.

4) Implement solutions that provide some buffer time to allow for a miss ship and redelivery attempt. This means an overnight solution should be qualified for 36 – 48 hours.

5) Data loggers should be utilized. Placement of data loggers should correspond with worse case areas of the payload as identified in the supplier’s qualification report. Understanding the correlation between product temperature and air temperature (what a thermistor based data logger will provide) can help in defense of product use given any slight excursion readings obtained. In many systems currently marketed it is common for air temperature readings just off the product surface to read as low as 1.6°C or as high as 8.4°C while the product itself is within 2°-8°C, but this varies depending on system and payload.

Biotech, Pharmaceutical & Medical Device Manufacturers (Commercial Shipments)

Biotechnology, pharmaceutical, and medical device manufacturers have their companies brand and reputation, as well as the health and well-being of the public, riding on the products they market. Regulation surrounding proper temperature control of commercial products has traditionally been most strongly focused on this segment versus downstream handlers of their products. There are several different ways that temperature sensitive therapies travel from manufacturer to end user. These include direct

distribution, where title is held by the manufacturer throughout the supply chain, and indirect distribution where title passes. Some manufacturers choose to outsource all or part of their distribution model while others choose to maintain in house control throughout.

Regardless of which distribution model is utilized manufacturers rank thermal performance as most important. While robust shipping solutions are utilized by manufacturers they have an advantage that is not typically available to the aforementioned shipment of clinical trial materials – stability data! Through the development process companies should be conducting ongoing stability tests on the formulations and products intended for commercialization (reference PDA Technical Report No. 53 Guidance for Industry: Stability Testing to Support Distribution of New Drug Products). Upon commercialization this stability data should be used wisely and, if possible, some stability should be allocated to the distribution segment of the therapies life cycle. Many variables are at play, but as a rule of thumb a 0.1°-10°C product could cost 40% less to package and ship when compared against a strict 2°-8°C product. When looking at expanding the temperature range of your product it is also important to understand that keeping a product from going below 2°C is much more difficult, and therefore more expensive, than keeping a product from getting to warm (i.e. above 8°C). Getting an allowance to ship at those two degrees between 0°C and 2°C can have a major impact on the packaging and logistics budget. Wider stability allowances provide more benefits than just reduced packaging cost.

Reductions in freight, warehousing costs, environmental impact and improved pack-out simplicity will also result. Commercial shipments often occur in well-defined shipping lanes. These lanes can be quantified accordingly and custom ambient temperature profiles can be created once enough data is gathered. Custom systems can be developed that are tested to less severe ambient temperature profiles than a pre-qualified clinical shipper which further results in decreased cost and waste.

Best practices to follow:

1) Conduct stability tests early and use this stability to reduce the cost and complexity of your temperature sensitive supply chain.
2) If strict performance (2°-8°C, 15°-25°C etc.) is required for distribution utilize whole number rounding when allowed (i.e. 1.6°-8.4°C is sufficient for 2°-8°C) per USP 34.
3) When shipping volume allows develop custom packaging efficiently tailored to your specific distribution lanes (ambient temperature profile) and products (package size, temperature range).
4) Monitor first mile commercial shipments through the use of data loggers while understanding air to product temperature correlations for the specific packaging configuration used.
5) Monitor last mile shipments through the use of temperature indicators mandating specific indicators to be used by third parties to protect your companies brand at minimal cost.

Third Party Logistics Providers (3PLs), & Wholesalers/Distributors

Companies in these categories connect the manufacturer of the therapy to the party responsible for last mile distribution (mail order & specialty pharmacy) or can send the therapy directly to a health care provider who administers or dispenses the medication through an onsite pharmacy. As the first point of handoff from manufacturers the companies in this segment traditionally operated under slightly less regulatory pressure and were subject to audits by the manufacturers of the products they distribute. The technologies and best practices employed by manufacturers have trickled down accordingly. Whether a company is classified as a wholesaler/distributor or a 3PL depends on whether title is maintained by the manufacturer (3PL) or transferred from the manufacturer (wholesaler/distributor). Many companies within this space operate divisions as 3PLs, distributors, and wholesalers: often operating the different business models out of the same facility.

These shipments are often monitored through the use of temperature indicators. When title has not passed the manufacturer exerts a heavier influence and often specifies the packaging that must be utilized while requiring temperature monitoring. Profit margins for companies operating in this space are tight and the cost of systems used is under constant pressure. These facilities often employ massive packaging
operations that are capable of changing pack-outs according to seasonal or even daily package destination based weather fluctuations. This operational flexibility allows them to utilize seasonally qualified systems, as opposed to universally qualified shipping systems, which results in lower system and shipping costs. Seasonal shipping systems help such companies to meet bottom line demands and package compliance but they must remain vigilant in the training of personnel to ensure seasonal pack-out changes are followed diligently and product is not compromised. More risk is assumed at this stage of the distribution process.

Best practices to follow:

1) When shipping volume is high enough it is recommended to develop custom packaging efficiently tailored to your specific distribution lanes (ambient temperature profile) and product order patterns (payload size and temperature range).

2) Consolidate multiple manufacturer products into a single family of packaging systems when possible to reduce storage costs, complexity, and variation that leads to pack-out failures.

3) Utilize pre-qualified or custom qualified systems tested with an appropriate range of min and max payloads in accordance with your wide product assortment allowing you to combine different therapies into a single package shipment.

4) Implement temperature indicators.

5) Repeatedly train and test personnel to ensure pack-out procedures are properly followed, especially for seasonality changes to system pack-out, refrigerant conditioning and staging.

6) Conduct a handful of live performance qualification (PQ) tests at the beginning of each seasonality change. Be sure to document these PQ’s for future audit defense.

Mail Order & Specialty Pharmacies

These companies operate solely in the “last mile” space. This is the final step in the distribution process that delivers therapies to the provider or patient directly.

These shipments are increasingly monitored for temperature performance through the use of temperature indicators. Chemical temperature indicators are the most prevalent in this space given the low cost point and ease of use. The trend to implement proper temperature sensitive packaging and utilize temperature monitoring devices in this segment is driven by many factors. Manufacturers, with their brand on the line, are increasingly encouraging or requiring the use of both qualified shipping systems and temperature indicators.

Regulation is increasingly focused on this segment. Improvements in packaging, monitoring, and best practices are also driven by accreditation bodies such as URAC. Pharmacy benefit managers (PBMs) are requiring proof of compliance through audits of packaging qualifications, shipping practices, and increasingly mandated use of temperature indicators. The importance of good temperature sensitive stewardship is spreading across this segment rapidly.

These companies are under extreme financial pressure to keep packaging and freight costs to a minimum. Seasonal shipping solutions, as opposed to universal pack-outs, are a given in this price sensitive arena. The mindset that “colder is better” has long prevailed at this stage of distribution. This is particularly dangerous since the majority of biological based therapies are actually damaged more during freezing events than excessive heat events. Qualified shipping solutions should always be used, but there are a few basic operational practices these companies can follow to ensure the most obvious and detrimental errors are avoided for refrigerated products.

Best practices to follow:

1) All six best practices for 3PL’s and wholesalers/distributors should be followed.

2) Qualified systems will detail proper pack-out, but here are some tips on packaging:
   a. Do not place frozen gel packs directly on product. Doing so can cause product to experience “cold shock” and dip below 0°C.
   b. Use a buffer material such as bubble wrap, insulation, or refrigerated gel packs between frozen refrigerants and the product itself.
   c. Allow frozen gel packs to acclimate at room temperature for a short period of time, typically 15–60 minutes, before pack-out. This secondary conditioning step is also referred to as “sweating” or “bench time” in the U.S. while the World Health Organization (WHO) provides similar guidance and calls this procedure “Thermal Conditioning”. Depending on the quality of buffer materials used this step can be eliminated.

3) A once prevalent and still common practice is to place the packed system into a refrigerator prior to carrier pickup to “help” the system perform. DO NOT DO THIS! This often causes product temperatures to drop well below 0°C causing more harm than good. Systems should be qualified to perform at ambient conditions.

4) Implement cold and hot temperature indicators in all shipments. The whitepaper titled “Think Inside the Box”, authored by Bill Bailey, RPh, COO of Citizens Rx, and Dan Kus, RPh, VP of Pharmacy Advantage, provides case studies on the effective use of temperature indicators in specialty pharmacy shipments. This report details the significant cost savings and customer satisfaction achieved and is available for download at www.coldchaintech.com.
Freight Forwarders & Couriers

These companies provide freight and logistics services to the clinical and commercial market. They are increasingly offering an in-house line of qualified shipping solutions which are sometimes privately labeled. In addition to robust thermal performance freight forwarders and couriers are often interested in designs that are freight optimized making the handling and placement of shipping systems on various vehicles and aircrafts as efficient as possible.

This makes their operations run smoothly and allows them to offer a better bundled cost for freight and packaging products. These companies are often involved in return re-use programs. As such they may require physically robust solutions that are capable of multiple shipments. With intimate knowledge of their shipping modes and lanes these organizations can often qualify packaging that works in their anticipated environments which improves system assurance at maximum cost efficiency.

Best practices to follow:

1) Utilize pre-qualified systems tested against ambient temperature profiles indicative of your typical hot and cold lanes.

2) For high volume lanes with consistent handling and well understood ambient temperatures consider custom qualifications, and even seasonal pack-outs, to reduce the cost and complexity of shipping systems.

3) Utilize data loggers in bulk and high value shipments to verify ongoing compliance.

4) Occasionally monitor ambient conditions of packages to verify no changes to handling that would impact performance and therefore the ambient temperature profiles qualified to.

5) If live actionable data logging is employed understand the impact of any unplanned intervention. I.E. if a portion of a refrigerated product appears to be trending warm ensure that placement in 5°C will not quickly drive the product below 2°C due to remaining frozen refrigerants. Detailed collaboration with your packaging supplier and understanding of the qualification data will help in implementing intervention SOP’s pursuant to live actionable data.

6) Provide both freight optimized and payload optimized options that cater to individual client needs.
Conclusion

Pre-qualified thermal shipping system claims cannot be accepted as marketed. Due diligence and methodical comparison of competing claims is the responsibility of the purchasing company.

Expertise from companies such as Cold Chain Technologies, Inc. can be leveraged in performing these comparisons through the use of proprietary advanced analytical tools, but some simple comparisons in each of these seven critical categories, and weighted as deemed appropriate by each organization, can help to provide a clear picture and apples to apples evaluation.

Author:
Jamie Chasteen
Senior Product Manager
Cold Chain Technologies

Contributors:
Nicole Stokes

References

¹ http://www.transparencymarketresearch.com/biologics-market.html
⁵ Georgia Tech & The Illuminate Group “Crucial Variables of Pre-Qualified vs Customized Temperature Sensitive Shipping Solutions” article published in Pharmaceutical Online
⁶ 2014 Report on Prescription Drug Costs by Prime Therapeutics

Cold Chain Technologies is a worldwide provider of thermal packaging product and service provider. Founded in 1967 to protect critical, temperature-sensitive product loads from the ups and downs of handling, weather, and other unpredictable events during shipment. Since then, the company has become an industry leader in innovative, performance-driven thermal packaging, designing, testing and manufacturing custom and off-the-shelf solutions for pharmaceutical, biotech, medical device, healthcare and food service companies. Distributed from multiple U.S. and international locations, CCT’s trusted brands include KoolTemp® GTS Pre-Qualified Shipping Systems, KoolTemp® Insulated Shippers and Koolit® Refrigerants, available in a wide range of duration and temperature ranges.