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Thermal Shipping Technologies: The Cold Hard Facts

Several years ago, we asked an independent testing lab to source the five most commonly used packaging technologies used by specialty pharmacies and evaluate their performance against a commonly used testing standard and the packaging manufacturer's own claims. In short, the outcome of this study and the data developed still holds true as many specialty pharmacies continue to purchase and use these same packaging technologies today.

The important points of this study are:

1. "Validated pack-outs" don't always provide the level of insulated protection as claimed (by the packaging manufacturer) and are often not engineered to endure excessive temperature exposure.

2. A Best Practice for pharmacies is to conduct PQ (Performance Qualification) testing specific to their geography and medications, to ensure that packaging is performing as expected – which includes testing under various weather conditions and shipping durations

3. Visual temperature indicators should still be used to:

- Alert patients to medication that has been potentially damaged by exposure to extreme temperatures during the shipment process.
- Reduce unnecessary medication reshipments due to patients subjectively thinking a medication is "too warm" or "too cold." Without a temperature indicator, it is impossible to know if an unacceptable exposure has occurred.
- Minimize unnecessary medication waste and uncertainty when shipments are delayed and go beyond anticipated time in transit. Temperature indicators can identify when medications are exposed to extreme temperatures.

Developing Good Distribution Practices at the Specialty Pharmacy

Gary M. Hutchinson, President Modality Solutions LLC

Overview

This paper presents highlights from a thermal performance study conducted by Modality Solutions LLC. The study examined theperformance of five shipping technologies commonly used by specialty pharmacies to transport high-value refrigerated specialty medicines against an industry accepted temperature profile standard.

Specialty pharmacies provide a specialized, comprehensive system of pharmacological care to patients with serious, chronic conditions and complex disease states. Their business is the management and distribution of high-cost, highvalue medicines that are not available through retail pharmacies. Unlike retail pharmacies, specialty pharmacies perform a broader range of services including more complex benefits investigation and prior authorization requirements, education/counseling services, patient assistance and compliance/persistence programs, and often serve as care coordinator and hub for patient interactions.

Manufacturers and payers recognize that specialty pharmacies have the skills and infrastructure to provide specialized shipping and handling for seamless delivery of important medicines directly to patients. These medicines, called “specialty drugs”, include biologics such as treatments for rheumatoid arthritis, treatments for hemophilia and blood disorders, anti-infectives, and chemotherapeutic agents.

They are more expensive than traditional pharmaceutical medicines and require special storage, shipping, and handling to ensure they stay within specified temperature range.

These drugs may also have unique inventory management or an FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) in place. A REMS may include requirements such as physician certifications, diagnostic results, physician/pharmacist training, and/or other requirements that must be met prior to dispensing the drug. Their use is on the rise and the trend is projected to continue.

Ten years ago, drugs dispensed by specialty pharmacies were primarily injectables; today, these can include oral drugs that are high-cost or for niche or orphan diseases. In 2009, specialty drugs accounted for 20% of all drug costs and by September 2012 that number increased to 28.7%.

By 2018, specialty drugs will comprise at least 50% of all drug costs.[1] Researchers forecast that total specialty pharmacy drug spend will increase from $290.00 per member per year to $845.00 by 2018.[2]

Since nearly all specialty drugs are temperature sensitive and require special handling, they are transported in packaging specifically designed to protect from exposures to temperatures out of the required range. Exposure to excessive heat or cold can diminish or even destroy drug potency, potentially causing serious downstream health problems for patients who may unwittingly administer temperature-damaged medicine.

To mitigate risks inherent in transporting temperature sensitive medicines directly to patients, particularly during extreme summer and winter temperatures, specialty pharmacies use thermal shipping systems that claim suitability for maintaining the temperature of refrigerated medical products during the first 24 hours of shipment. The performance of several thermal systems was the subject of a recently conducted independent study.

Purpose

1. Evaluate five commonly used shipping technologies by specialty pharmacies in direct-to-patient deliveries for thermal control performance to assess how well they maintained a specific temperature range within a 24-hour period.

2. Assess the value of a visual temperature indicator to show conformance to a predetermined temperature range; if a shipment took longer than the 24 hours and/ or the temperature exposure exceeded the shipping system allowance, a temperature indicator technology would provide the temperature monitoring and alert the patient to potentially damaging temperature exposure.

Study Design/Methodology

Five thermal control technologies were tested in a controlled laboratory setting to determine if the thermal capabilities of the technology, according to the manufacturer's claim of temperature control within a 24-hour timeframe, were met.

This baseline testing to manufacturer claims could then be used to assess whether visual indicators would be valuable for late shipments that required longer than 24 hours for delivery.

The following commonly used shipping systems were tested:

- Insulated bubble bag
- Insulated box liner
- EPS molded cooler
- Insulated envelope
- EPS panel sheet cooler

All are used by specialty pharmacies to protect temperature-sensitive products for directto- patient delivery. These technologies were packed to manufacturers' recommendations and tested against the ISTA 7D thermal profile.

This profile is a public testing standard for thermal packaging and is commonly used by pharmaceutical manufacturers to test thermal control capabilities.

The study examined performance of the technologies during seasonal extremes of winter and summer as simulated by ISTA 7D thermal profiles. An additional 6-hour interval was added to the test to evaluate performance in the event the package was not delivered in the allotted 24-hour timeframe. The major package delivery services deliver to a number of ZIP codes that pose challenges for next-day service.

None of the five tested thermal packaging systems typically used by specialty pharmacies to protect temperature-sensitive products for direct-to-patient delivery maintained the specified temperature in the first 24 hours. All five performed below expectations when tested to the ISTA 7D industry standard. Most did not perform against their own published claims.

The lack of performance in the first 24 hours highlights the need to look at new packaging technologies and visual controls for use by specialty pharmacies.

The performance results during the additional 6 hour period (24 to 30 hours) are vitally important. The data sheds light on thermal system performance to temperature excursions in the "last mile" when shipments are most vulnerable — when medicines are delayed or left unprotected and exposed at the last stop in the cold chain e.g. mail boxes and on front porches. The need for visual indicators is more acute, especially for mail order specialty pharmacies shipping selfadministered specialty drugs, because caregivers or patients who self-administer medical treatments at home have no accurate way to identify potentially temperature-compromised medicine.

Why target 2°C to 8°C?

The US Food and Drug Administration guidance stipulates that temperature controlled biologics be stored and transported at labeled storage conditions of 2°C to 8°C unless stability data is available to support storage at other temperature ranges. Manufacturers also target 2°C to 8°C as guidance for storing temperature-sensitive products. Specialty pharmacies could ship shortterm outside the labeled storage conditions if they have permission from the manufacturer or they have access to stability data for the drug.

Because there is risk of late shipments in difficult to service areas, additional controls and monitoring may be necessary to ensure the ability to maintain 2°C to 8°C. The concern regarding maintaining drug quality during shipment is particularly important during winter and summer seasonal extremes. The ISTA 7D 24-hour cycle thermal profile was extended by 6 hours to simulate these seasonal extremes for shipments that may be left unprotected at doorsteps or in mailboxes during home delivery.

Conclusion

Analysis of the data found the technologies tested provided limited thermal control and allowed a wide range of temperatures outside of the typical labeled storage conditions for medical products that require refrigeration. The thermal exposures outside of 2°C to 8°C were of two types:

- the short initial period of thermal equilibration
- the effect of the temperature cycle on the packaging system

None of the technologies tested maintained 2°C to 8°C without some excursions during the first 24 hours. During seasonal extremes (both winter and summer as simulated by the ISTA 7D thermal profile), additional controls and monitoring will be required to verify the 2°C to 8°C range is maintained.

With direct-to-patient deliveries, specifically in difficult to service areas where shipments could take longer than 24 hours, additional controls would be necessary with all five technologies when maintaining temperature during shipment is required.

Visual temperature indicators shipped with the medicine are valuable tools for specialty pharmacies and patients to use to easily identify if products have been exposed to temperatures outside of their specified limit.

Temperature indicators that clearly alert patients to temperature breaches help to avoid administration of medicines that may have become ineffective, lost potency or that might pose a potential safety issue.

Discussion

It's true that well-designed, high performance thermal packaging systems can help mitigate risks to temperature-sensitive products. But their thermal control properties are limited, leaving gaps in the cold chain and opening up the possibility of temperature-compromised goods reaching unsuspecting patients. The good news is that specialty pharmacies can better support a standard of care for patients who rely on them to help manage their difficult diseases and treatment regimens.

Manufacturers need to determine whether there are adequate and secure controls in place at the specialty pharmacy to receive and ship pharmaceutical and biologic products that require special handling. Evaluate the specialty pharmacies managing your drugs to ensure the best cold chain processes are employed to protect both product and patient.

Specialty pharmacies need to select appropriate technologies based on verifiable test data. Require your packaging supplier or an independent third party to qualify packaging solutions to a public standard thermal profile using pharmaceutical industry best practices.

Require management review of on-time delivery performance by ZIP code for package delivery services to identify challenged areas. Be realistic about on-time delivery performance expectations and choose packaging accordingly.

Qualify your shipping lanes to ensure performance is as expected across all types of weather conditions and seasonal extremes through the last mile. For example, follow current weather conditions and understand what is happening within those shipping lanes to anticipate delays or extreme weather, and adjust accordingly.

There is a tremendous amount of value to be gained by incorporating reliable visual indicators into 'last mile' cold chain logistics networks. Some indicators can be affixed directly to individual units to show the end user (patient or caregiver) whether the product was, or was not, exposed to excessive heat or cold outside the specified shipping limit. These devices can address the concerns of manufacturers seeking assurance and proof that shipments are monitored, and of patients looking for confidence that their medicines have been maintained within the specified temperature range during delivery.

References:

[1] http://www.primetherapeutics.com

[2] http://www.artemetrx.com

Results

The Cold, Hard Facts:
What You Need to Know About Thermal Shipping Technologies

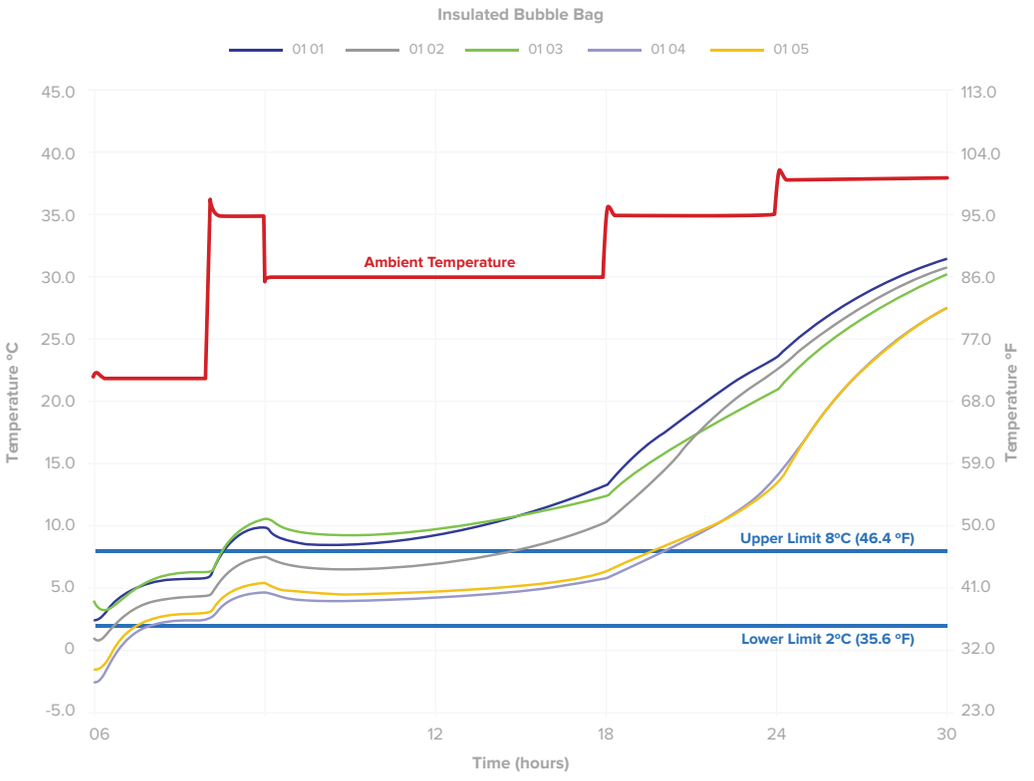
Heat Cycle / Summer Profile Tests

This paper presents highlights from a thermal performance study conducted by Modality Solutions LLC. The study examined the performance of five shipping technologies commonly used by specialty pharmacies to transport high-value refrigerated specialty medicines against an industry accepted temperature profile standard.

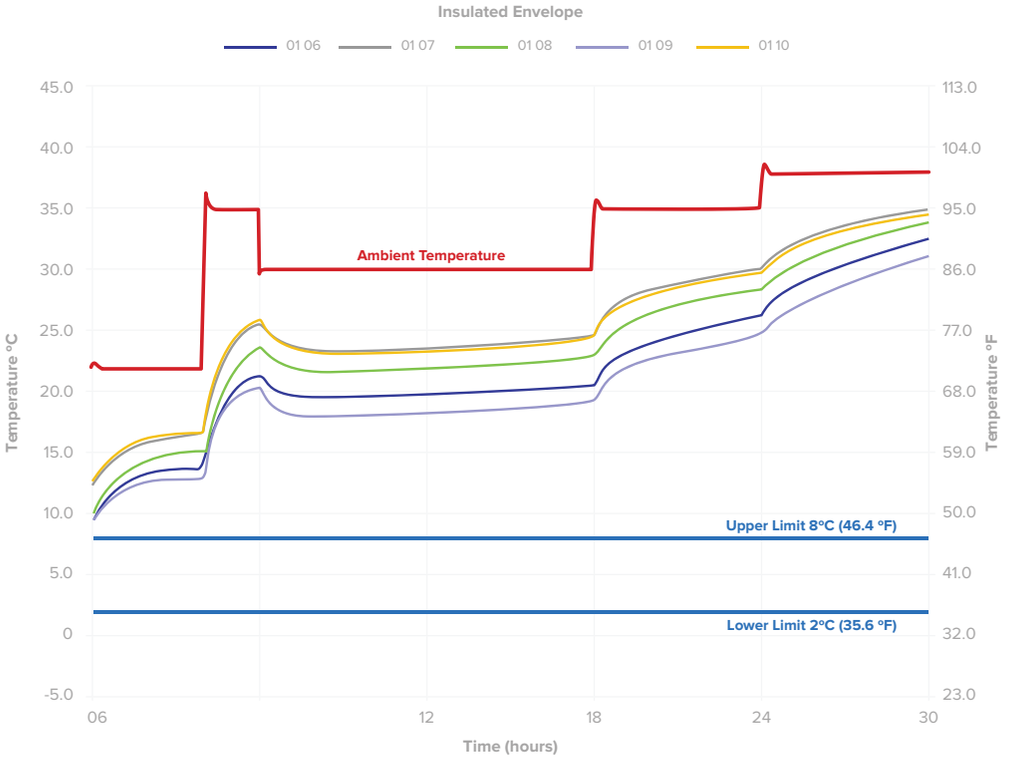
Heat Cycle/Summer Profile Results:

During the heat cycle, all five technologies failed to maintain temperature within recommended range. Four of the five reached sustained temperatures that were too warm – two within the first six hours of the simulated shipment. One was too cold and would have immediately frozen the specialty drug placed inside.

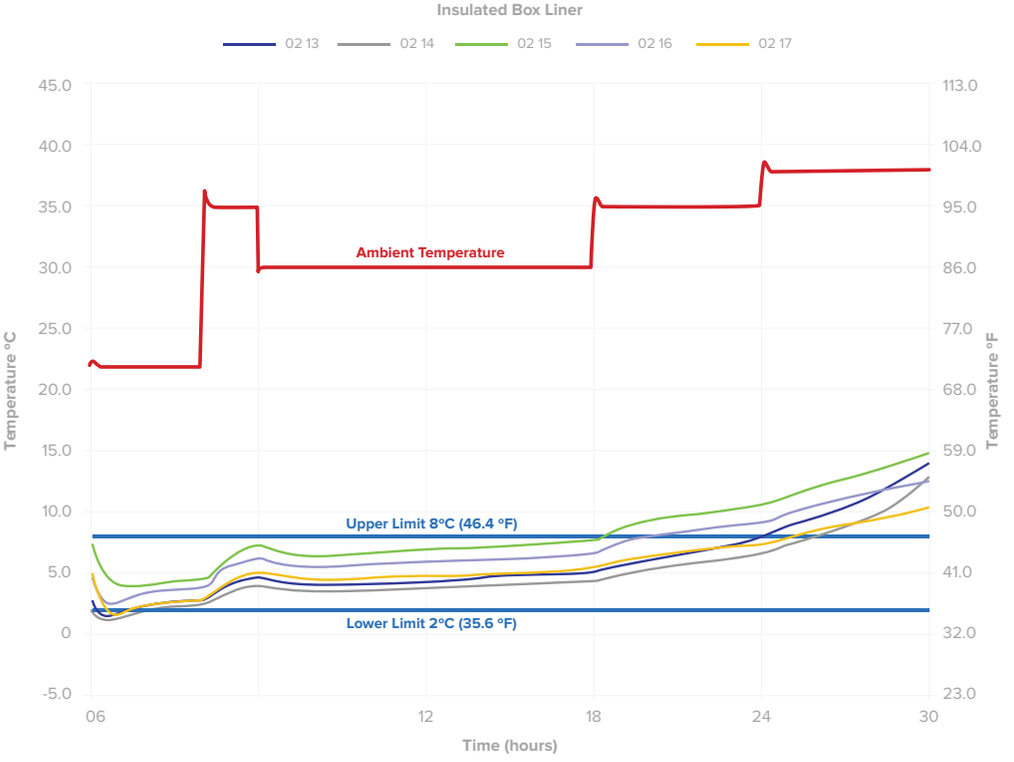
1. The Insulated Bubble Bag failed to provide adequate thermal control during summer profile testing.



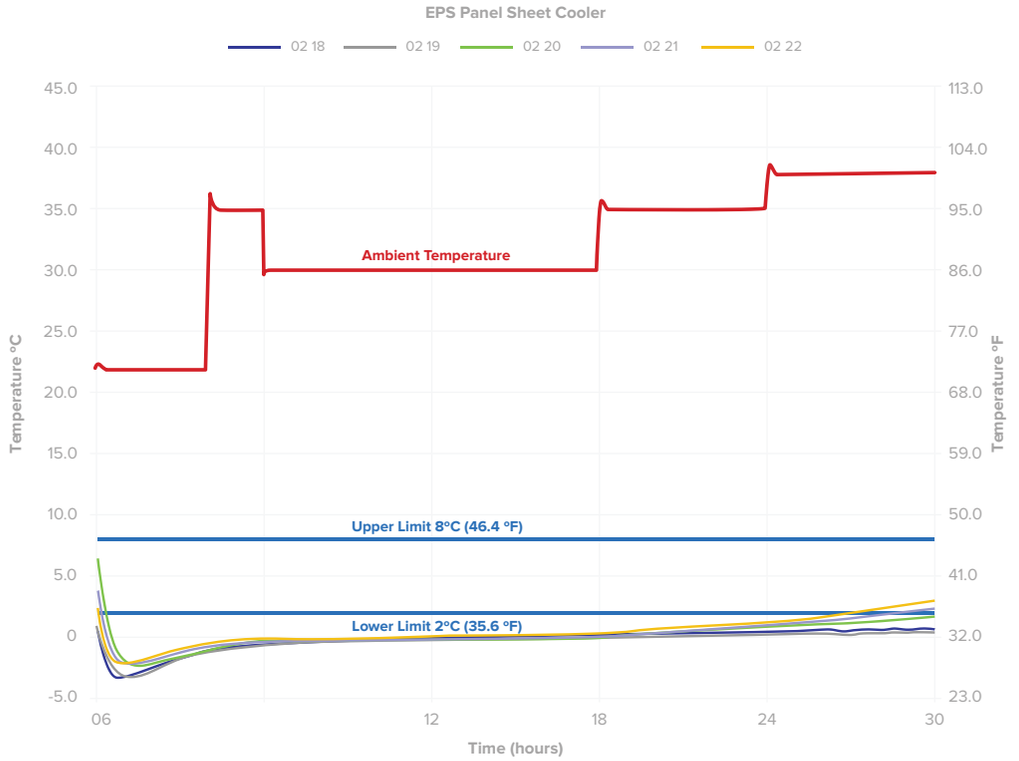
2. Summer profile testing demonstrated the Insulated Envelope provided negligible thermal benefits.



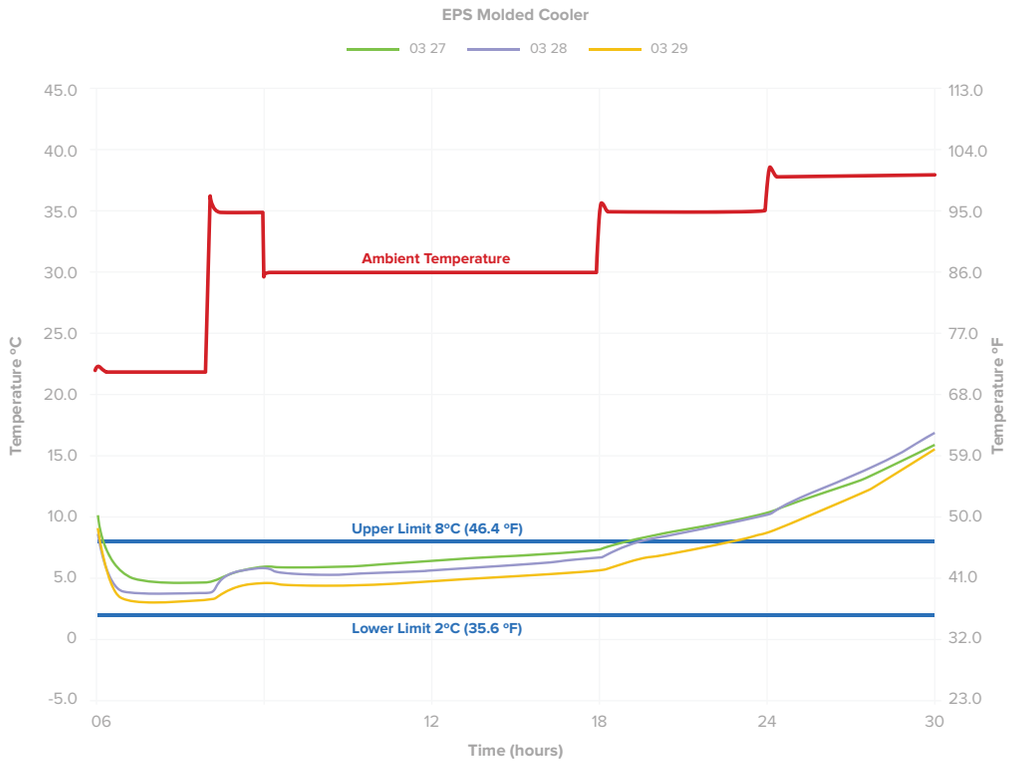
3. Insulated Box Liner technology provided appropriate thermal control for 18 hours; temperature excursions were recorded in the 18 to 24 hour interval.



4. Pack out design flaws in the EPS Panel Sheet Cooler allowed the simulated drug product to freeze and remain frozen for the 24 hours.



5. The EPS Molded Cooler held temperature for 18 hours; thermal excursions occurred during the 18 to 24 hour interval during summer profile testing.



Results

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Cold Cycle / Winter Profile Tests

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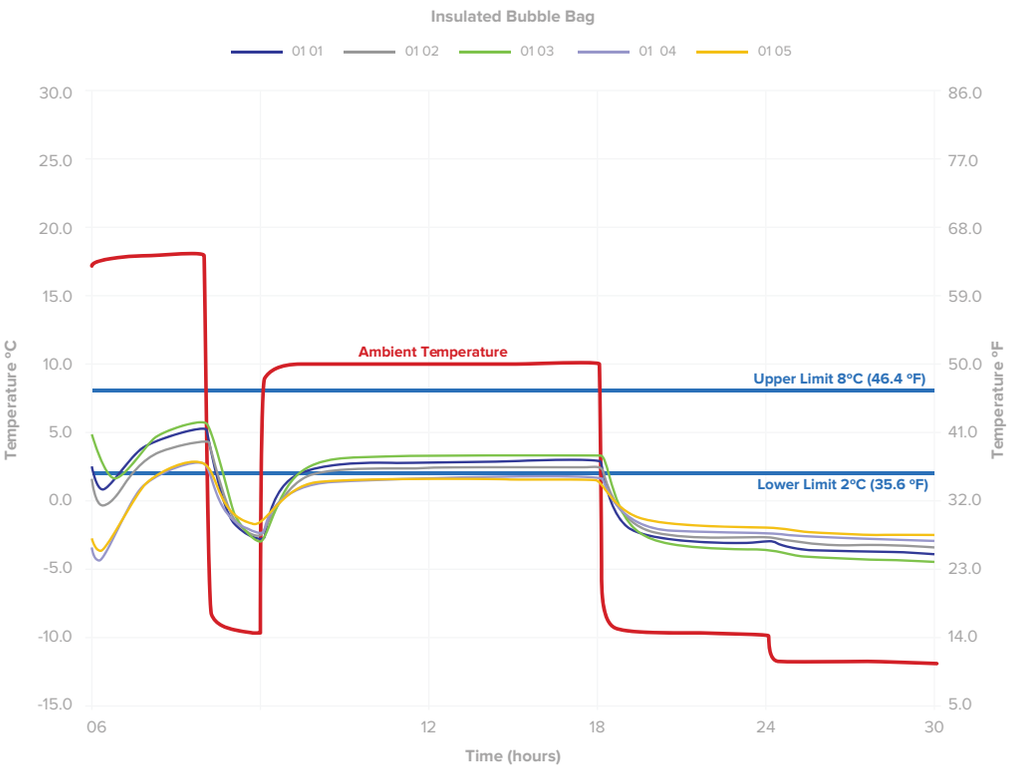
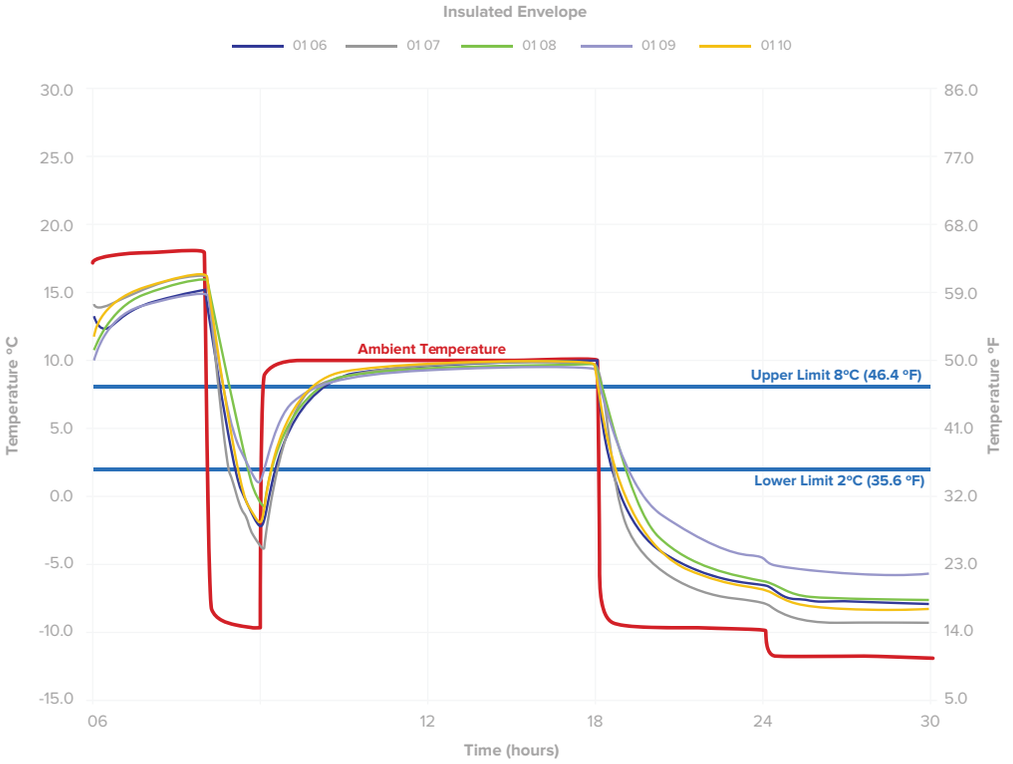
Cold Cycle/ Winter Profile Results:

Each of the technologies tested performed outside of the recommended 2°C to 8°C range and temperatures for all five dropped below freezing which resulted in frozen product. Three of the technologies have the potential of inducing multiple 'freeze-thaw' events in the specialty drug; the multiple phase changes of liquid formulations are extremely hazardous to drug quality and nearly impossible to detect at time of receipt or use by the patient.

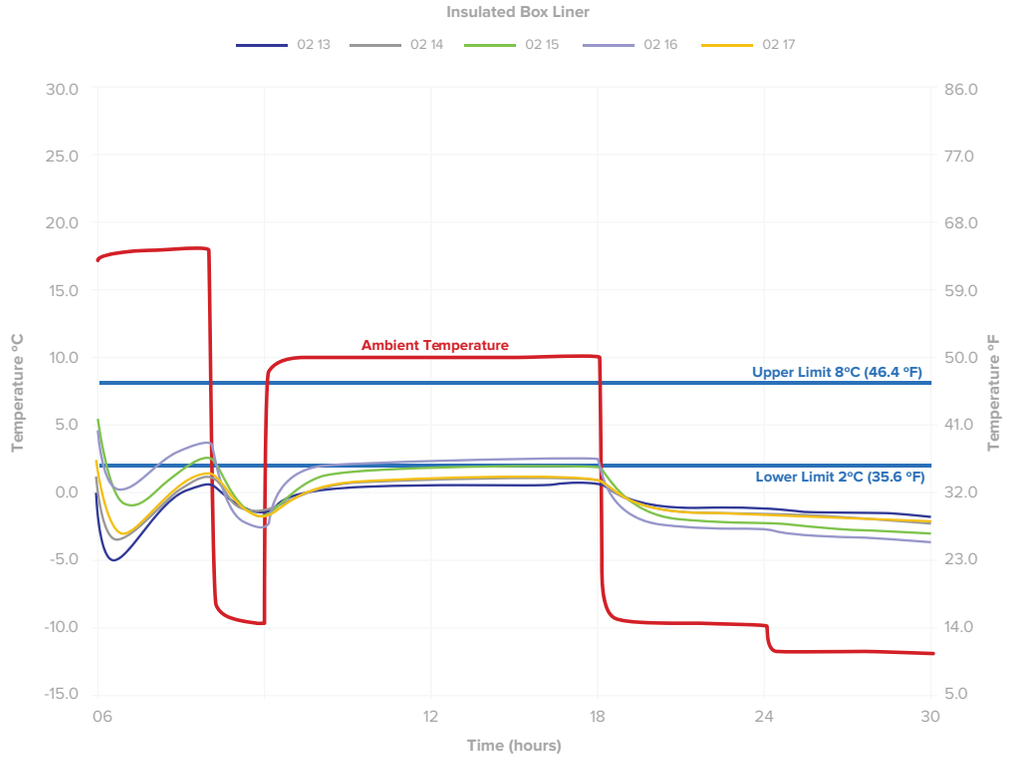
1. Freezing and low temperature excursions for the entire shipment are a concern in winter profile testing with Insulated Bubble Bag technology.



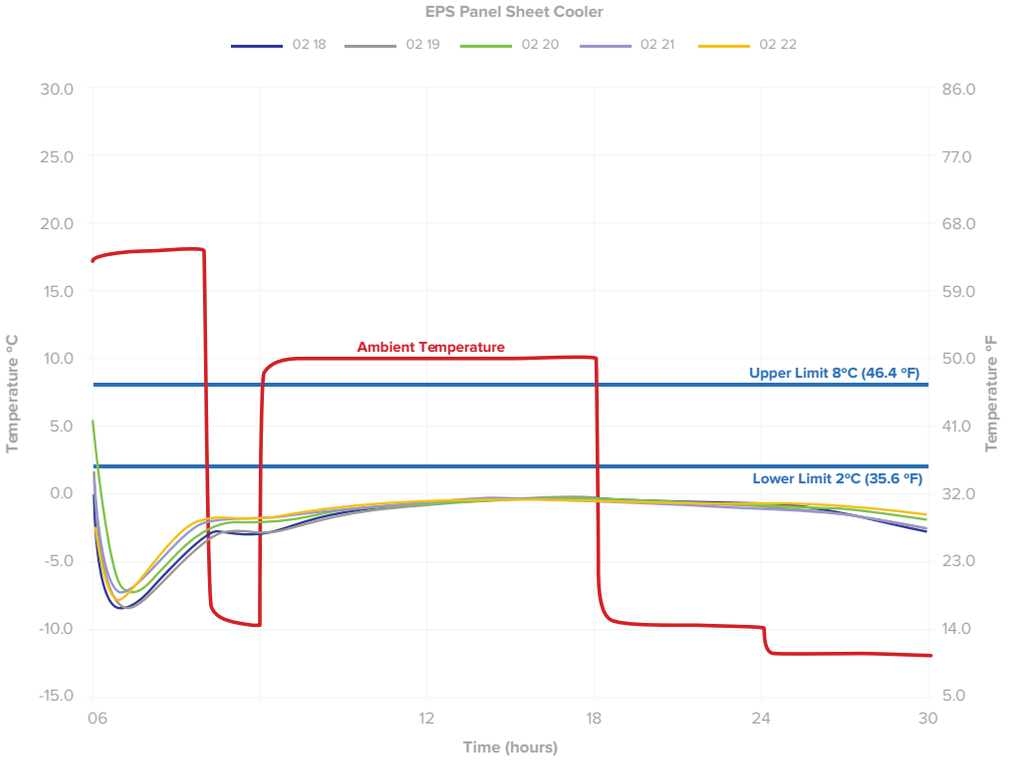
2. Two 'freeze-thaw' cycles and elevated temperatures make Insulated Envelopes unsuitable for winter season shipping.



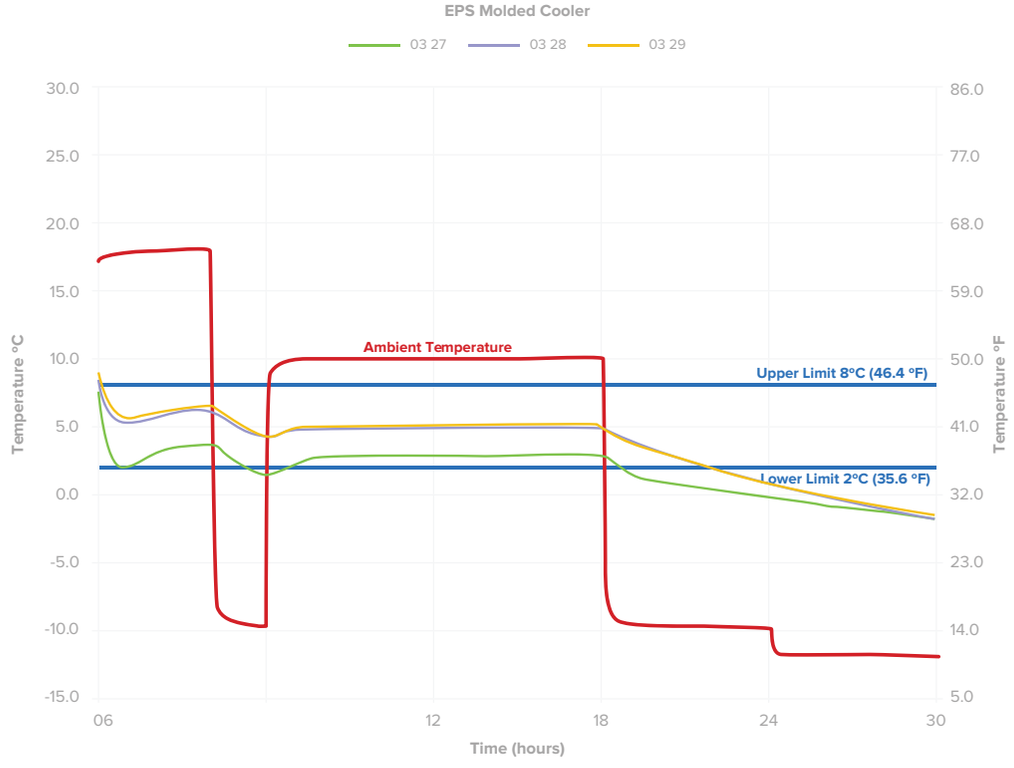
3. The potential for multiple phase changes of the drug product elevates risk for products shipped in Insulated Box Liners during the winter season.



4. Due to design flaws in the EPS Panel Sheet Cooler, product freezes and stays frozen during the entire shipment during winter profile testing.



5. The EPS Molded Cooler performed best during winter profile testing; however, temperature dipped out of range in less than 20 hours.



It should be noted that the surface temperature measurement conditions in this study were recommended as real-life scenarios observed in the field by Safe-T-Vue users performing validations. The recommended procedure for validation appropriately measuring the internal core temperature is described in Control Doc #3032 COMZ Suggested Validation Procedure for Safe-T-Vue 10 and Doc# 3032 COMZ Suggested Validation Procedure for Safe-T-Vue 6.

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