CardinalHealth
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Cold Chain Packaging

Cold chain — refrigerated tote qualification

The performance qualification for refrigerated tote packaging used at Cardinal Health is designed to maintain refrigerated pharmaceuticals within their labeled storage environment of 2-8°C (36-46°F) during shipment.

Materials

To ship refrigerated pharmaceuticals, Cardinal Health uses plastic totes with an expanded polystyrene (EPS) liner for insulation. We have replaced the traditional frozen water-based gel-packs with a safe and very effective phase change material contained in pillow-like panels. Phase change materials liquefy or solidify (freeze) at specific temperatures. The phase change materials will recharge as ambient temperatures fluctuate, making them ideal for maintaining a 36- 46°F environment within our refrigerated totes. The orange panels start their journey refrigerated (to protect from freezing conditions) and the green panels start out frozen (to protect from heat). The orange panels absorb the energy from the green panels (as well as external winter temperatures) and begin to solidify (freeze) at a temperature of approximately 39°F, protecting the product from experiencing temperatures below the labeled range. As the temperature inside of the tote changes, the physical state of panels changes between solid and liquid in order to maintain 36-46°F within the tote during shipment. The phase change panels require pre-conditioning before each use (orange in a refrigerator and green in a freezer). Large totes require 2 orange and 2 green pre-conditioned panels and small totes only require one orange and one green panel. To protect the product from freezing, the orange panels must always be placed next to the product and the green panels must never be placed next to the product. Pharmaceuticals are placed inside a bag to protect from possible condensation or panel leaks. The phase change panels are derived from 100% renewable resources, are non-hazardous/non-toxic, and have been submitted, tested, and approved by the USDA as a bio-preferred product. Additional panels are used in some markets for additional transportation time or extreme heat.

Qualification Process

Over four years of lab and field testing was conducted to ensure the delivery of a performance qualified system that will maintain refrigerated pharmaceuticals in a 2-8°C environment regardless of the season or geography and regardless of the amount of product shipped, from a single vial to a full tote. Redundant environmental laboratory testing was conducted following industry acknowledged and accepted engineering test standards utilizing industry recognized winter and summer temperature profiles. Temperatures were recorded with calibrated thermocouples placed directly on the payloads located in the most thermally vulnerable locations within the tote. The qualification standard included strict compliance to 2-8°C without excursions. The small and large tote performance qualifications were conducted by an ISTA (International Safe Transit Association) certified environmental chambers laboratory under strict test protocols.

Small Tote

Limitations of Spot Temperature Testing

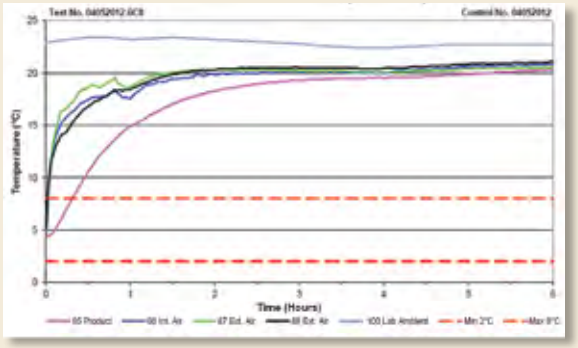
Cardinal Health uses refrigerated totes with a passive coolant system opposed to an active system like a freezer. Active systems respond to rapid temperature changes, such as when a door is opened, by engaging the compressor and fan to replace warm air with cold air until the temperature is brought back within the set range. Passive systems are designed to remain closed until the product is removed for storage. When the phase change panels are initially placed into the totes they are at the optimal temperature to maintain the product within the 2-8°C temperature range for the period of time that the totes are qualified for (cycle time) when exposed to winter or summer temperatures during transportation. Passive coolant systems utilize an energy source and insulation to maintain the desired temperature range. This system utilizes phase change material and expanded polystyrene (EPS) liners with lids, which are contained within the plastic tote. If the tote is opened, the cool air is immediately replaced with warmer air and the phase change panels may not have enough energy remaining to bring the temperature back within the desired range, especially at the end of the cycle. Therefore, opening the tote, even for as few seconds to place a temperature probe inside and closing it again will not provide realistic results.

Additionally, the use and placement of temperature measuring devices can result in grossly inaccurate readings for several reasons. One of the most unreliable temperature indicators is Infrared (IR) guns. These devices are typically accurate within 2°C (3.6°F) when properly calculated. IR guns are commonly used to determine heat leaks in construction. Another problem with end of cycle spot temperature testing is related to the surface temperature changes of packaging, such as the common paperboard cartons for pharmaceuticals. Paperboard is porous and has a very low thermal conductivity. Glass, on the other hand, has a high thermal conductivity (more than 6 times that of paperboard). This means that paperboard does not conduct heat well, and it adapts (changes) to new temperature environments very quickly. These properties were demonstrated in certified environmental laboratory scientific tests.

In addition to monitoring and recording the refrigerated and ambient temperatures, the following was also recorded:

1. product temperature (thermocouples on liquid filled glass vials),
2. the airspace temperature inside the paperboard carton (thermocouples in the corner dead space), and
3. the outside surface of the paperboard cartons (thermocouples on the outside surface of the box). The product s contained in the manufacturer's paperboard carton with the aforementioned probes were placed and held in an environmental chamber until they all reached 4.4°C, at which time they were placed into an ambient lab environment at 22°C.

Cardinal Health product probe temperatures vs. air probe temperatures corrugate carton — minimum product load constant lab ambient (22°C ± 3°C)



The difference between the product temperature and the outside surface of the paperboard carton over time is as follows:

1. At 3 minutes the carton surface temperature had gone above 10°C while the product surface was still below 4.5°C (variance of 5.5°C),
2. At 10 minutes the carton surface temperature was above 16°C and the product was a 6°C (variance of 10°C),
3. At 15 minutes the carton surface temperature rose to 17°C and the product was still below 8°C (variance of more than 9°C),
4. At 30 minutes the carton surface temperature was above 18°C and the product was at 11°C (a variance of 7°C),
5. At 60 minutes the carton surface temperature reached 19°C and the product was at 15°C (a variance of 4 °C),
6. At 120 minutes the carton surface temperature rose above 20°C and the product was approximately 18°C (a variance of 2 °C)

This test clearly demonstrates the impact of the thermo conductivity differences between glass vials (containing liquid product) and the outside of the vials in the paperboard carton surface temperatures. These examples are at the beginning of the qualification time cycle when the product and the environment within the tote are in the 4°C range. Obviously, closer to the end of the delivery cycle the temperature inside the tote will be higher (although still below 8°C); therefore, carton surface temperature may be above 15°C when removed from the tote as a result of the low thermo conductivity of paperboard, while the product will still be below 8°C. In summary, using an IR gun to determine product temperature at delivery time has compounded inaccuracies due to the device's accuracy as well as the paperboard carton surface versus product temperature variances.

Supply Chain Integrity

In order to ensure the integrity of the supply chain, Cardinal Health maintains proper storage of our refrigerated pharmaceuticals in qualified storage environments that are monitored and alarmed with calibrated devices. Our associates are trained and phase change panels are pre-conditioned using controlled processes which are subject to internal as well as regulatory audits to ensure compliance. Proper packaging will be evaluated upon return of any product and must include the signed Ongoing Assurance Form, confirming that the product was maintained in the labeled storage refrigerated conditions and has been prepared and packaged properly for authorized return. Instructions for return are provided to our customers on the back of the Merchandise Return Authorization form as well as at www.cardinal.com/coldchain, along with informative videos, information, instructions and Frequently Asked Questions about the cold chain process at Cardinal Health.

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