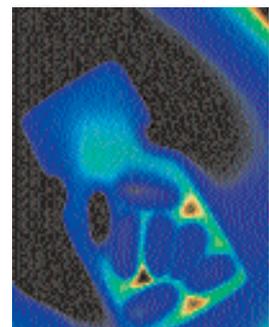


Packaging Helps Protect

Temperature-Sensitive Products

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Regulators seek proof of product protection from temperature abuse in pharmaceutical packaging.

Protecting a product from temperature abuse is gaining importance as the number of biopharmaceutical formulations grows and regulators look for proof of product stability throughout the distribution process. In the absence of cold chain management standards, the Parenteral Drug Association's Pharmaceutical Cold Chain Discussion Group (PDA-PCCDG, Bethesda, MD) has released a draft guidance, "Medicinal Cold Chain Guideline."

The purpose of the document is to "provide guidance ... on the essential principles and practices of transporting temperature-sensitive medicinal products through the transportation environment. Comments were due to PDA by 15 January 2004.

Packaging plays a critical role in ensuring that a product is maintained at the proper temperature throughout the distribution chain. Cold chain issues most likely to generate warning letters or 483s related to a lack of documentation, a lack of qualification of temperature monitors, package design, or procedures.

The guidance document grew out of a discussion group formed in 1999 at an industry-sponsored meeting and evolved into the PDA-sanctioned PCCDG in 2002, currently chaired by Rafik Bishara, PhD, director, Quality Knowledge Management and Technical Support, Eli Lilly and Company (Indianapolis, IN), who also leads PDA's Stability Interest Group. Members include representatives from 19 other companies.

"The need for control is implicitly stated in 21 CFR Part 211.110," Bruce Meiklejohn, biopharmaceutical product development at Eli Lilly and Company, told an audience at PDA's spring meeting in 2003. Europe is more specific in guidelines about Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03).

The guideline describes a three-step process—

identification, development, and implementation and includes a glossary of cold chain terms and appendices describing conditions for studying stability, temperature excursion, and thermal cycling.

Principles for qualifying the transport of temperature-sensitive medicinal products mirror the guidelines and regulations that are used for manufacturing. Operators should take into account potential exposure to temperature extremes as the result of distribution delays, environmental system failure, or other events.

Successful qualification requires manufacturers to

- develop specifications, processes, systems, and components
- write procedures
- approve protocols and reports
- justify test methods and acceptance criteria
- qualify testing that challenges "anticipated extremes"
- perform ongoing monitoring or periodic evaluation
- control change.

One of the most important considerations is to perform stability studies to determine the degree of temperature abuse that can be tolerated because the acceptable temperature range for transport "may differ from the conditions specified for long-term storage." Recommended studies include long-term and accelerated stability studies as outlined in ICH Q1A, a temperature excursion study and a thermal cycling study. With stability results in hand, a stability limits document can be drafted.

The next step qualifies distribution packaging and systems via thermal challenge testing that mimics the conditions that the package is likely to encounter during shipping. Factors to consider include environmental conditions at the origin and destination points, seasonal variations, transport routes and modes, and transit time.

"Whenever possible, environmental profiles should be based on realistic expectations of transport temperatures, which are developed using scientifically sound criteria. This may be done using field testing and monitoring of actual shipments,

Companies represented on the PCCDC*

| | |
|----------------------|-----------------|
| Abbott | Jansen |
| Amgen | Eli Lilly |
| Aventis | Merck |
| Astra Zeneca | Novartis |
| Bausch & Lomb | Organon |
| Baxter | Ortho |
| Boehringer Ingelheim | Pfizer |
| Centocor | PSGA |
| Genentech | Schering-Plough |
| Genzyme | Wyeth |

*PDA Letter, Vol. XXXIX, No. 11, November 2003, p. 9.

review of historical environmental data, review of published standards (i.e., ISTA 5B, *Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging*, published by the International Safe Transit Association, East Lansing, MI) or other means.”

The design of primary and secondary packaging components also influences the effect of temperature abuse and the design

of the transportation container and/or system. With environmental profiles and packaging components identified, a functional requirements document summarizes critical parameters such as transportation duration, modes and routes, product stability, and primary and secondary packaging.

The next step defines product impact components such as insulated containers and refrigerants that have a direct influence on temperature control. This packaging system undergoes design testing to show it is likely to provide the appropriate level of protection and qualification testing to confirm that it works. According to the guideline, “Qualification testing and results should be documented in a formal report.”

Operational qualification (OQ) and performance qualification (PQ) protocols, test plans, or standard operating procedures should define the testing objective, scope, materials description, equipment description and calibration information, critical quality attributes, critical perfor-

mance parameters, test methods, and acceptance criteria. OQ testing depends on calibrated temperature monitors, which are placed directly in the test shipment at enough points within the load to collect sufficient data to quantify the conditions experienced by the product during its travels. Multiple tests should be performed to ensure reliable results. PQ testing then confirms the process is effective and reproducible under field transportation conditions. Once the process is qualified, approved procedures are written, and personnel are trained.

As stated in the guide, “The final step in cold chain management, quality systems, provide a high degree of assurance that the qualified transportation systems will continue to perform as intended.” Quality systems include approved written procedures and specifications, a calibration program, a stability program, a qualification program, a deviation and investigation program, a corrective and preventive action program, a training program, peri-

odic cold chain process assessment, and a change control program.

Packaging-related components

Protecting a temperature-sensitive product requires several packaging-related components such as temperature monitors, insulated containers and refrigerants.

Available in a variety of formats from several suppliers, temperature monitors have

been available for more than a decade. Similar to many technology-based products, current models tend to be more powerful and less expensive than their predecessors.

Perhaps the least expensive products are pressure-sensitive labels, which permanently change color when a certain temperature is reached so that recipients or caregivers can tell at a glance whether the product has been temperature abused and

can estimate how long it has experienced the threshold-exceeding conditions. Sometimes referred to as a time-temperature indicator (TTI), this type of label can be automatically applied on standard labeling equipment. Available in a variety of styles and triggering temperatures, monitoring durations range from a few hours to a couple of weeks. Some designs can indicate more than one triggering temperature. Costs are influenced by the style and the quantity ordered and typically range from less than \$1 to more than \$2 each (MonitorMark Time Temperature Indicators, 3M, St. Paul, MN; Irreversible Temperature Labels, Telatemp Corp., Fullerton, CA; WarmMark Temperature Indicators, IntroTech, Loenen, The Netherlands; Vitsab Temperature Labels, Vitsab Division, Cox Technologies, Inc., Belmont, NC).

A TTI that is especially designed to monitor vaccine vials is widely used on the polio vaccine and meets the requirements of international organizations such as the World Health Organization and UNICEF. Its color-changing coatings are based on diacetylene monomers, and the top layer of the structure is pharmaceutical-grade paper (HEATmarker VVM, Temptime Corp., formerly LifeLines Technology, Inc., Morris Plains, NJ).

Somewhat more sophisticated are battery-powered strip chart devices, which track temperatures for a certain number of days by marking a roll of pressure-sensitive paper. Many of these units are capable of being reloaded and reused (TempCheck Temperature Recorder, Marathon Products, Inc., Modesto, CA; Ryan Universal Transit Instrument, Ryan EZT, Ryan Universal K, Sensitech, Inc., Beverly, MA). Others are designed to be one-trip devices (Tamperproof Transit Thermometer, Telatemp Corp.).

Digital data loggers are even more sophisticated. Prices range from approximately \$35 to \$150 per unit. One logger in a key-shaped plastic housing features read/write memory, a digital thermometer, a real-time clock, a nonresettable counter, programmable high- and low-temperature thresholds, and light-emitting diode lights that indicate whether temperature requirements have been maintained. Activation can be immediate, up to 45 days away or when brought into contact with a control unit.

Sampling intervals can range from 1 to 255 min. A serial interface allows the device to display the data in log or histogram format (CyTherm Temperature Data Logger, Dynasys Technologies Inc., Clearwater, FL).

A number of other suppliers provide similar units (TempTale, Sensitech, Inc.; DataSource, Cox Technologies; Flash-Link In-transit Data Loggers, Delta-TRAK, Inc., Pleasanton, CA). Low-cost, disposable digital recordkeepers also are available (TagAlert, Sensitech, Inc.; c/temp Single-Use Temperature Data-loggers, Marathon Products).

At the conclusion of a trip, a data logger often is returned to the vendor where the data are downloaded and delivered to the customer on a disk or through an Internet portal. If a problem occurred during shipment, vendors also may provide claim verification services.

A new monitoring option based on radio frequency identification technology also is developing. As pharmaceutical companies comply with Wal-Mart and US Department of Defense mandates and apply

RFID tags to pallets, cases, and items to automate handling and enhance the tracking of product through the supply chain, it will become possible to add functionality to the tags. One possibility is active temperature recording.

Similar to their TTI and data logger counterparts, insulated shippers and refrigerants are available in various formats from a variety of sources. Often the two are used together, but one or the other alone may provide sufficient protection in some situations.

Refrigerant choices include the old standby, dry ice, water packs, or blankets, which can be chilled or frozen, and gel packs or blankets. The latter contain phase-change material that freezes at temperatures other than 0 °C. Blankets consist of multiple fluid-filled pouches and offer flexibility. In some cases, the water or gel packs or blankets can be reused, which reduces the cost per trip. Printing to provide brand identity or other information also is a possibility (Coldpak Reusable Gel Ice, Flexible Ice Blanket, Cryopak, Industries, Vancouver, BC).

One gel-based product is based on carboxymethylcellulose and is housed in blowmolded containers or pouches that incorporate an antimicrobial additive to discourage bacteria, mold, and mildew growth that can cause odors (Ice-Pak ice substitutes, Ice-Pak Group, a wholly owned subsidiary of Cryopak).

Insulated packaging materials include expanded polystyrene foam, similar to those often seen in disposable picnic coolers; honeycomb corrugated, foil-lined corrugated, or foil-laminated bubble pack liners; and vacuum-insulated panels. Several vendors offer more than one option (Eastern Seaboard Packaging, Huntersville, NC; TechPak Solutions, Peabody, MA; Packaging Solutions, LLC, Monroe, LA; SCA Thermosafe, Michigan City, IN).

Making the right selection of components depends on the same elements that are needed for successful cold chain management. "Know your product, know your process, document your process, review your process," concluded Meiklejohn. **PT**