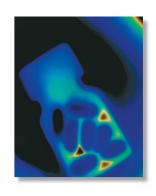
Cold Chain Concerns

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RFID and batterypowered
containers are
among the
developments
receiving
attention in the
pharmaceutical
cold chain.

anaging the cold chain not only keeps products at the proper temperatures, but it also can increase supply chain efficiency and reduce costs. A close-up look at the cold-chain operations of Mayne Pharma (Melbourne, Australia, www.maynegroup.com) illustrates these benefits. Raymond Jenkins, global demand and logistics manager at Mayne Pharma's regional head office in New Jersey, cut shipping time from the company's manufacturing site in Australia to Dallas, Texas, from 10 days to less than 72 hours, saving his company \$300,000 per year. Drawing on 20 years of materials management experience, Jenkins did his homework and discovered that goods were sitting idle in customs waiting for import clearance. So he created a shipment template harmonized to the tariff schedule. It clearly lays out each product's chemical abstract and FDA identification numbers, the name of each drug, and how it is used. As a result, customs inspectors immediately see the information they need to speed up the clearance process, (e.g., that the contents contain no animal products and are finished goods for human use not intended for further processing). In the first six months after instituting this procedure, only one Mayne Pharma shipment out of more than 70 was held up for examination at the point of entry.

For cold deliveries, Jenkins had relied on foam sheeting inside corrugated cases. This packaging provided an R-value of less than 10 and only protected the product for ~10–12 hours. He currently uses custom-designed expanded polystyrene (EPS) inserts. The top and bottom inserts measure 2-in. thick and the side inserts are 1-in. thick. By helping prevent gravity from pulling the coldness right through the bottom of the box, the extra thickness produces an R-value of 18–22 and keeps products at the proper temperature for 36–48 hours.

Jenkins outsourced validation testing to an independent third party. First, he got his quality assurance and compliance departments to agree to a protocol incorporating relevant standards (*e.g.*, IATA DGR Section 2.7.9) that cover such specifics as positioning of the temperature monitors inside the packaging. Then, summer and winter trials were conducted at a target product temperature of 2–8 °C. Although keeping products from freezing in

winter can be difficult, Jenkins says that summer is the biggest challenge. "The temperature inside trucks can exceed 120 °F in a very short time," he says.

Relative humidity also was monitored during the trials because it makes cold packs sweat and lose cooling capacity more quickly. Jenkins used nosweat gel packs, which come with cloth wrappings that absorb moisture and prevent product damage. Through a combination of package testing and drug-stability studies, Jenkins found he could economize by using EPS packaging and second-day air to protect his products in winter conditions.

Jenkins now is considering whether to switch to condensed foam and foil packaging (**True Pack**, New Castle, DE, www.truepack.com). The multiple layers deliver a superior R-value of 40 and keep the contents cold for five days. This packaging would allow product to be shipped by ground transportation if the quality assurance department approves, he says.

In another project, Jenkins is testing packaging that uses battery power to effectively turn containers into little refrigerators. These packages can be plugged into an airplane's electrical system to maintain refrigeration and monitoring during a flight (**Kelvin Technologies**, Dallas, TX, www. kelvintechnologies.com).

The regulatory scene

Currently, no federal regulations define cold-chain packaging standards. Individual FDA inspectors, however, have begun to write Form 483 citations for temperature violations on the basis of their own subjective notions of how to apply the FDA's general authority to regulate the safety and efficacy of drugs. FDA is reportedly working on cold-chain requirements, and other groups are working to develop specific guidelines.

The **PDA's** Pharmaceutical Cold Chain Discussion Group (PCCDG, Bethesda, MD, www.pda. org) posted for comment a draft advisory guidance regarding cold-chain processes and testing more than a year ago. As of 1 January 2005, the document, "Medicinal Cold Chain Guideline," remains in draft form, according to George Robertson, PhD, PDA's vice-president of science and technology.

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A PDA committee is in the final phase of reviewing comments from its technical advisors. The process is lengthy because the guidance is meant to be a ground-breaking document that would, for the first time, spell out cold-chain packaging standards in some detail. The committee is now wrestling with competing notions of how much detail to provide. One school of thought argues for specific standards while other participants

believe the document should be left more general, Robertson says.

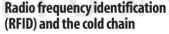
The initial draft contained a lot of field-specific terminology. More explanatory language is being included in the final version because the end result is intended to serve as a practitioner's document, Robertson says. Robertson expects PDA to issue the guidance sometime in 2005.

The work of the United States Pharma-

copeia (USP, Rockville, MD, www.usp.org) touches on various aspects of the cold chain. The USP has some mandatory standards pertaining to cold-chain packaging such as the storage and packaging definitions contained in chapters $\langle 661 \rangle$ "Containers" and $\langle 671 \rangle$, "Containers—Permeation." In addition, it has informational guidelines for controlled thermal packaging in chapter $\langle 386 \rangle$, storage, shipping, and distribution handling in chapter $\langle 1079 \rangle$, and good packaging practices in chapter $\langle 1177 \rangle$.

Europe does not have specific cold-chain standards yet, either. *The European Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)* state only that drugs requiring temperature-controlled storage should be transported by appropriate and specialized means.

The PDA discussion group is partnering with Europe's Cold Chain Committee (C3), which is writing a strong guidance for the continent. Participants hope to harmonize the two efforts with the eventual goal of having a single standard published by the **International Conference on Harmonisation** (ICH, Geneva, Switzerland, www.ich.org), according to a source close to the PDA group.



RFID is being widely adopted to track and trace all manners of products and is seen as a potential tool for cold-chain management.

There is strong interest in RFID. Although McKesson Corp. (San Francisco, CA, www.mckesson.com), the nation's largest pharmaceutical wholesaler, is not currently using the technology in the cold chain beyond track-and-trace, that scenario could quickly change. McKesson is primarily waiting for RFID-reader technology to improve and prices to decrease, according to Ron Bone, McKesson's senior vice-president for distribution support.

One cold-chain products and solutions vendor, which counts most of the top pharmaceutical companies in the country as customers, is running an RFID cold-chain pilot project. The RF-enabled monitors are placed inside test packages to record temperature and humidity at specified intervals and wirelessly download the data to a Web-accessible database when they pass a reader. Active, self-powered tags (*i.e.*, wireless sensors) are being used in the pilot, but commercial solutions could incorporate



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passive tags and bar codes as well. The pilot does not feature global positioning, but whenever a tag passes a reader, time and temperature data are transmitted along with location and shipment status (**Sensitech,** Beverly, MA, www.sensitech.com).

Herein lies the benefit of RFID for the cold chain. With near real-time reporting and e-mail alerting of temperature trends inside a package, a distributor can take ac-

tion if a temperature violation is about to occur. If the maximum allowable temperature has already been breached, the customer can be alerted and a new package can be shipped proactively instead of waiting for the customer to report that the product went bad. Temperature tracking and trip history are completely visible without first having to retrieve and read monitors buried inside shipments.



Added benefits

RFID advocates claim RF-enabled temperature monitors are more accurate than colorchanging labels or strip charts. Fewer shipments are destroyed because in marginal cases, the data stream allows quality engineers to decide whether the product is still potent. It also cuts out fingerpointing because it provides proof of when and where temperature limits were exceeded. For fragile products, shock and vibration sensors can be added. Finally, RF-generated information can help logistics managers save on coolant and attendant dead-weight shipping costs because packaging can be closely matched to the conditions the shipment is likely to face.

Preventing product loss can add up to real money. "In one real-world case I'm aware of," says Henry Ames, director of life sciences marketing at Sensitech, "an entire shipment of biologics was frozen, causing an \$8-million loss."

CSL (Parkville, Victoria, www.csl.com), Australia's biggest pharmaceutical company, is using an RFID-based temperaturesensing system that features a read-write, credit-card-size, 13.56 MHz active tag, which can be attached to or inserted in shipments. Other components include RF readers, software, and a Web portal to a secure database. The tag can be programmed to register temperatures within a certain range at specified intervals or locations and can be set to log all data points or just exceptions. Alerts are provided whenever data are uploaded or an exception occurs so that corrective action can be taken. The active tags reportedly cost less than traditional data loggers and may be reused for 12 months or until battery power is depleted. Future tag designs may measure additional environmental conditions such as humidity, shock, and vibration (x Tract Consignment Monitoring Service, Global Licensing & Innovation, a Carter Holt Harvey Co., Reservoir [Melbourne], Victoria, Australia, www.glandi.com).

Other cold chain management solutions

Using RFID is not the only way to protect temperature-sensitive products. Other options include implementing data loggers, color-changing labels, and insulated packaging (see *Pharmaceutical Technology*, March 2004, p. 36).

Data loggers typically require downloading to a personal computer. One reusable,

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button-shaped digital logger, however, simplifies data transfer by interfacing with a low-cost reader. The reader, in turn, transmits data directly to a printer to generate a one-page shipment history (model PT Instant Certificate Maker, **Photologic Ltd.,** Cobourg, Ontario, www3.sympatico.ca/photologic/cdw.htm).

Another system combines a data logger with a proprietary, reusable insulated shipping container. The vacuum-insulated panel construction of the container maintains shipment temperatures in the 2–8 °C range or <0 °C for five days while an "onboard" computer monitors conditions. The system also relies on a turnkey logistics service and an e-commerce Web site that provides access to shipment data (Cold Chain Shipping Container, **Kodiak Technologies, Inc.,** Kingsville, Texas, www.gokodiak.com).

Insulated containers are available in various formats including box liners, pallet covers, and pouches. The seven-layer structure includes aluminum foil to reflect heat, polyethylene for strength, and bubble material to block heat flow. The thin, light-

weight material can be customized to match temperature-control requirements. It also can be reused and can be stored in 85% less space than EPS foam insulating material (TempShield thermal insulating material, **Reflectix, Inc., a subsidiary of Sealed Air Co.,** Markleville, IN, www.reflectixinc.com).

Color-changing labels include various structures such as irreversible temperature-indicating labels and time temperature indicators (TTIs). Irreversible temperature-indicating labels provide a permanent record of temperature abuse. Typically, these labels are designed to register across a span of temperatures and are inexpensive and easy to use (Thermostrip Irreversible Temperature Indicating Labels, Hallcrest, Inc., Glenview, IL, www. hallcrest.com; Thermax Indicators/Strips, Thermographic Measurements Ltd., Flintshire, UK, www.t-m-c.com). A simpler version consists of a spot label that changes color and sometimes reveals a message if its designated temperature is exceeded, providing "good/no good" information at a glance (Clearing Point Label, Hallcrest; Chill Checkers, Thermographic Measurements).

A newcomer to the TTI field offers a twostage pressure-sensitive label construction, which activates with the application of a spot activator label over the indicator printed on the base label. These labels change color over time as shelf life winds down or if the product is temperature abused. Currently in use in the seafood industry, this two-stage construction eliminates the need to store the labels in a refrigerator or freezer before use, a typical requirement for color-changing TTIs. Three standard labels address various temperature requirements, and custom structures also are available (TT Sensor, Avery **Dennison Industrial Products Division**, Strongsville, OH, www.industrialabels. averydennison.com).

These are still early days for cold-chain management. But with the sale of temperature-sensitive biologics growing at a healthy clip, it's a safe bet that technological innovation will continue and that temperature-controlled packaging will come under increased regulatory scrutiny. **PT**

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