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Keeping Watch

Monitors along the cold chain could alert users to any harmful excursions.

By Daphne Allen, Editor
and David Vaczek, Senior Editor

In October 2006, shipments of Fluvirin influenza vaccine by Novartis arrived at Cardinal Health Care “in either a frozen state and/or below the required storage temperature,” according to a statement on FDA’s Web site. The frozen Fluvirin, which was supplied in 5-ml multidose vials bearing the Chiron Vaccines label, apparently didn’t put patients at any particular risk other than having to be revaccinated. Novartis hasn’t named the cause of the temperature excursion.

Are your products vulnerable to a similar occurrence? Worse yet, could your products be subjected to such change yet appear to be acceptable upon receipt?

Experts say that a robust package that will hold up under the worst conditions can be designed. But is it possible to protect them against all distribution uncertainties? Could monitoring that package as it travels along the cold chain give you the ultimate peace of mind?

NONSTOP MONITORING?

Manufacturers of high-value products particularly vulnerable to damage or diversion may want to keep a close watch over them. Larry Gordon, president of Cold Chain Technologies (Holliston, MA), says that products always face some risk after they leave a manufacturer’s control. “In the world of temperature control, you design and test your package in a simulated environment. But anything can happen in the real world,” he says. “You

could end up with ice storms.”

Gordon says that in 1999 the United States Pharmacopeia (USP) debated whether monitors needed to be on every product shipment. While makers of temperature monitors were thrilled at such a potential requirement, drug firms wanted to be able to decide for themselves what was appropriate.

USP’s General Chapter <1079> Good Storage and Shipping Practices says in the section titled, Shipment from Manufacturer to Wholesaler, “Where necessary, a monitoring device for temperature and/or humidity should be used during shipping and distribution.”



Intellex’s semipassive RFID tags feature 300-ft read ranges and 64 kilobit of extended memory.

While FDA has no requirement for in-transit tracking, the agency has reminded industry that manufacturers bear most of the burden of keeping adulterated drugs—which includes drugs damaged through temperature excursions—off the market. In the September 2006 issue of the *Gold Sheet*, FDA’s Nicholas Buhay, acting director of the division of manufacturing and product quality in the Center for Drug Evaluation and Research’s Office of

Compliance, explained that “mapping of the shipping, equipment, data collection during shipment. . . [has] application.” However, the agency has “not reached the point where we would be saying that these things will be expected.”

As a maker of temperature monitors, Gordon is careful not to recommend monitors for every package. “Whether to use a monitor is an internal decision. They are not the first line of defense. They just give you the ability to double-check your temperature-control solution.” He says that manufacturers of products “so critical that they cannot afford to have any losses may benefit from such monitoring.”

“There are so many variables in distribution environments—it is hard to control them all,” adds Henry Ames, director of strategic marketing, Sensitech Inc. (Beverly, MA). “It is impossible to know 100% that your products were not exposed to excursions, unless you monitor them.” He adds that most drug manufacturers have some sort of ongoing monitoring program, ranging from monitoring every package to periodic sampling of their distribution network.

William Hingle, marketing manager for TCP Reliable Inc. (Edison, NJ), says his firm “recommends that each shipment be monitored to ensure that the product has stayed within the predetermined temperature boundaries. This may not always be possible, given the direct or indirect costs associated with monitoring every shipment. Usually the decision is based on product value should it need to be replaced and/or the



Escort loggers have a bookmark feature that places a mark at certain data points when a magnet is touched to the unit. This is handy to track when boxes go through sorting centers, distribution points, etc., says Don Pagel of Kodiak.

length of time it will take to replace it.”

To help companies monitor their shipments, Cold Chain Technologies markets KoolWatch, a battery-operated electronic device that indicates product temperatures during transit. Cold Chain programs the disposable units to a product's temperature limits and then checks the unit's temperature-reading ability against a NIST-traceable reference. KoolWatch's shelf life before deployment is three years, and once activated, its onboard battery functions for two years.

Parameter settings include two high and low temperatures and high and low excursion temperatures; delay start times (0–99 minutes) and sampling intervals (1–99 minutes) are possible. The KoolWatch can be programmed to report whether product exceeded time or temperature limits. It can also be used to trip should a limit be exceeded just once.

But these are not “data-recording devices that enable you to download temperature data,” says Gordon. “The KoolWatch indicates whether the product temperature met programmed criteria at particular sampling times.”

Sensitech offers TagAlert electronic indicators and TempTale data loggers. “Indicators provide a record of an excursion, based on preprogrammed limits, but they provide no data log,” says Ames. “Electronic data loggers do build a time and temperature log of excursions.” The firm's Cold Chain Manager

software used to collect the data from the company's TempTale data loggers is 21 CFR Part 11 compliant.

Kodiak Thermal Technologies Inc. (Houston) also offers programmable onboard loggers for excursion monitoring. “We use Escort data loggers with a standard RS-232 connection. We are one of the very few that monitors every shipment for both internal and external data,” says CEO Don Pagel. “That means that receivers can know about excursions even before opening the box, which can allow them to refuse it without opening the container.” After shipments, a user can plug into the logger and download all the data for that shipment or just leave it running for multiple shipments.

All of Kodiak's containers are available with these loggers. “But we also sell them without loggers, because some customers have already validated their own choice and use their validated drop-in logger,” adds Pagel. “The problem with a drop-in logger compared with our onboard loggers is that our onboard loggers give both ambient and internal temperature readings, whereas the drop-in logger can only give internal temps. If the payload experienced a temperature excursion, you would want to know what was going on outside the container as well.”

RFID ENTERS THE FIELD

Ames of Sensitech says, “One of the strongest value propositions for

radio-frequency identification (RFID) in the pharmaceutical industry will be in the cold chain, because high-value biologics are the future of medicine. The rate of adoption will be driven by the intersection of the regulatory environment and opportunities for return on investment.” Ames offered that prediction in a recent electronic newsletter from *PMP News* (ePackage Newsletter; December 20, 2006). Sensitech markets an active-RFID-tag system called TempTale RF in conjunction with its Cold Chain Manager application. Monitor data are automatically uploaded to remote servers and onto a Web-based central repository. Users receive views of time, temperature, and location data that are segmented for the graphic illustration of events. Users can monitor processes and temperature patterns in near to real time and receive automatic alerts via cell phone or pager messaging, for such details as a temperature drifting out of range. Segmented data can be analyzed for tracing deviations from standard operating procedures arising in supply-chain handling, says Ames.

“When an excursion occurs with a [standard] data monitor, you are getting the information after the fact. You have to go back and look at the logistics information to recreate the shipment,” Ames says.

RFID technology can enable cradle to grave content and compliance data on a shipment, a package, or even a unit of dose, adds Michael Petersen, COO, Information Mediary Corp. (IMC; Ottawa, ON, Canada). Shipments of refrigerated goods can be tagged with the firm's Log-ic temperature-tracking tags. Temperature profiles can be downloaded via wireless RFID readers, RFID reader gates, and desktop RFID readers.

Log-ic tags are available either as trackers capable of 64,000 temperature readings (sufficient to monitor a vaccine vial box for the life of the product, says the firm) or as full data loggers capable of recording 8000 time and temperature points. The water-resistant, flexible

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Class 3 EPC RFID sensors measure 2 × 2 in. by less than 1/10th in. thick and have an active life ranging between 45 days and 3 years, depending on the configured mode.

Intellex Corp. (Santa Clara, CA) offers battery-assisted semipassive RFID tag and reader technology as a lower-cost solution than active tag systems for applications such as tracking plant assets and parts used in production processes. Richard Bravman, chairman and CEO, says Intellex's semipassive tags and readers also provide advantages in package tagging and cold chain management. The company's InfoSure tags and I-Beam fixed interrogators support longer read ranges compared with passive tags, and feature extended memory for storing product and shipment data locally on the tag. (For more information, see the sidebar on page 54.)

When it comes to RFID, says Petersen, companies often confuse RFID-enabled temperature sensing with RFID-enabled item tracking. "They are similar, but not really related," he says. And people are also confused by standards, he adds. "A lot of niche applications can benefit greatly today by not adhering to all standards. For instance, IMC has developed its suite of RFID-enabled Intelligent Active Packaging on the 13.56-MHz HF RFID standard, but not in strict adherence to all ISO standards. That's to make our products less expensive, more flexible, and scalable in high-volume manufacturing environments. However, IMC does offer the ability to other reader and infrastructure companies to integrate our proprietary protocols into their reading devices. Some standards are outdated, while others lack the required infrastructure to fully implement."

IMC argues that standards should not drive specifications or needs, but rather the ultimate need should drive new standards. "A lot of applications require no standards, but simply smart integration and interoperability with other systems and solutions," says Petersen.

Pagel says that Kodiak is investigating RFID. "But there are still two issues

with RFID that are limiting our use. First is the continued lack of a standard. Second, we would need to use active RFID tags for distance reading, which is still an issue with the FAA because they may continue to transmit during flight."

Sensitech has configured its tags to a "reader-talks-first" protocol. "Hence, the monitor wakes up and listens for a particular network," explains Ames. "The monitor will not transmit data unless it senses that it is in its own network. Thus, Sensitech's TempTale RF monitors meet FAA requirements for use on airplanes."

"To use RFID effectively, we would also need to have programmable tags that would be continually updated by the data logger so that each read would give the up-to-date information from the RFID tag," says Pagel. "This is already an existing technology, and once we resolve the other issue, it would not be a problem to do this. We are also considering short-range technologies such as Bluetooth as an alternative."

The costs associated with a particular device, along with the degree of accuracy and length of time or intervals between readings, drive what type of device is best suited for a particular shipment, says Hingle. "RFID technology is interesting to many in that it offers additional tracking features. This type of technology can also be used with real-time tracking programs that would enable managers to know the status of their shipment during its transportation. This information can be of huge value in making decisions before a shipment has been compromised. It can reduce or eliminate the time a shipment is quarantined after its arrival at a destination."

WHY MONITOR?

Most companies monitor both internal (product temperature) and external (ambient temperature) during thermal shipping studies, reports Sensitech. These data are used to "create a thermal profile of the actual shipping environment defining expected extreme thermal variation, both high and low.

Once the information is collected and evaluated it is used in packaging design, development of pack-out requirements, and documentation of SOPs," explained Sensitech's Ken McCabe at a recent meeting of the Institute of Packaging Professionals' Southern California chapter held at DDL West (Costa Mesa, CA). "Thermal mapping and shipping studies will help reduce the risk throughout distribution, enabling companies to maintain product quality and efficacy," he emphasized.

So why monitor packages beyond testing programs? If companies invest in distribution studies and in qualifying and validating a transportation package that they feel will withstand distribution hazards, why would they then need to track a package they are already confident in?

These questions bring to mind the debate over whether shipping containers can truly be validated—or just qualified. "Performing distribution studies and validating a package provides a given set of variables that will always follow the same parameters," says Hingle. "As this is not always possible, the term *validation* has been replaced with qualification of a package to account for assumed variables. Practically all parties involved in the transportation of a temperature-sensitive package know that Murphy's Law is always present. Monitoring the shipment is one way for managers to make informed decisions regarding their product should there be a possibility the temperature integrity has been compromised."

Whether to gather transit data "is a risk-based decision," says Ames. "There is value in using data loggers all the way across the supply chain. But companies need to evaluate product risks versus product and distribution costs." That said, he adds that concerns about product quality, patient safety, and brand reputation should be more than enough to justify monitoring. ■