Sharing Stability Data and Shipping Outside of Label Claim

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Director of Strategic Marketing, Sensitech

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Increased regulatory focus on the drug distribution environment is expected to draw attention and help clarify regulations and standards for temperature-sensitive products. It will also likely drive manufacturers and their supply-chain partners to work together closely to define product-quality-related expectations and required documentation.

While U.S. Pharmacopeia <1079> Good Storage and Shipping Practices states that supply-chain partners work together to protect product quality and ensure patient safety, sharing stability data is generally not an accepted protocol. Regulatory authorities support the argument. Accurately managing temperature excursions in later stages of distribution provides opportunities to increase downstream partner compliance, reduces costs, and improves patient safety.

The primary challenge of managing cold chain excursions is that typically no comprehensive temperature log accompanies a product from the manufacturer to the point of dispensation. Without a full temperature history, serial downstream distribution partners cannot determine whether temperature excursions exceed cumulative limits determined by stability data. Given that, multiple agents could wrongly conclude that the product was maintained within limits and is acceptable for use. This position was supported by Ian Holloway, manager, defective medicines report centre, UK Medicines and Healthcare Products Regulatory Agency (MHRA), at the 2009 IQPC Cool Chain conference in Brussels. Holloway raised concerns for issues related to parallel imports, however, the theme is the same. A legitimate concern is that more than one supply-chain partner will use the same allowable excursion.

Sensitech's TagAlert

REGULATORY EXPECTATIONS

The regulatory expectation is that medicinal products will be shipped at label claim unless sufficient data are available to support expanded temperature exposure. A great challenge that the pharmaceutical supply chain faces when considering distribution of drugs outside of label claim, however, is that regulations differ dramatically by country and, sometimes, by region within a country. Even individual expectations can vary by auditor. For example, Mexico, Brazil, and Taiwan have a reputation for strictly holding product to label claim during distribution; other countries, however, are open to a reasoned position supported by science. The MHRA and FDA are often viewed as taking this latter approach. The MHRA has repeatedly stated that "The Qualified Person should not release the product unless it complies with the marketing authorization and he/she is convinced that it has not been damaged during transportation. Supporting data would normally have been filed in the regulatory package and been formally approved by the regulator." [2]

From a regulatory perspective excursions beyond label claim need substantiation by drug stability data, and documentation must also support the potential effects on the container, closure, and label. Regulatory agencies have expressed concern that thermal and humidity variability can negatively affect these items.

DRUG DISTRIBUTION

The U.S. Federal Food, Drug, and Cosmetic Act Chapter V section 501 subchapter A Drugs and Devices, (a)(2)(B) states: A drug or device shall be deemed adulterated—"if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with CGMP . . . [because] holding of the drug occurs when the drug is being distributed, transported [or] warehoused for distribution or transfer."[3] So CGMPs apply in the pharmaceutical supply chain. This clear regulatory expectation and concern for how drugs are stored, handled, and transported in later stages of the supply chain has led to FDA's increased focus on drug distribution. At the Parenteral Drug Association's Pharmaceutical Cold Chain Interest Group meeting held in Berlin in late 2008, Rosa Motta, compliance officer, division of manufacturing and prod-

uct quality, Center for Drug Evaluation and Research (CDER), at FDA, stated that FDA would begin auditing the distribution environment. This is significant as, to date, FDA has left distribution environment auditing to the individual State Boards of Pharmacy. This increased focus on drug distribution has caused manufacturers and their supply-chain partners to work together closely to define product-quality-related expectations.

SHARING STABILITY DATA

Sharing stability data raises a number of concerns for pharmaceutical manufacturers and regulators. First, most manufacturers feel that few of their downstream supply-chain partners can accurately interpret and utilize detailed stability data. Second, sharing such data could enable quality-related decisions to be made without consulting the manufacturer. Third, if a manufacturer were to publish expanded shipping temperatures, this information could be used multiple times or not documented—leading to patient safety concerns.

Most industry leaders would argue that manufacturers take a conservative approach to managing the supply chain for temperature-sensitive medicinal products. In general, a manufacturer's internal quality system defines control limits for thermal variability. The manufacturer's exception management system is then referenced in managing any thermal excursion. Allowable excursion rates are defined and there is an exception reporting process that captures variability. Deviations that fall outside of the predefined allowable excursion limits, often beyond label claim, trigger a corrective action and preventative action (CAPA) and root cause analysis (RCA) process. In the case of a temperature excursion falling outside the predefined allowable range, the product impact is researched on a lot-basis and compared against stability data. Product disposition is then documented justifying further distribution or destruction.

SHIPPING CONDITIONS

Without broader shipping temperature guidance for downstream supply-chain partners, pharmaceutical manufacturers have placed a higher level of compliance and cost onto later stages of distribution. In other words, the distribution environment is largely held to label claim while pharmaceutical manufacturers often rely on their quality system and stability data to allow for predefined excursions.

This challenge is significant because either the distributor will not monitor thermal variation in the distribution environment, or the distributor will choose to comply with label claim storage conditions—thereby increasing packaging and logistics costs.

In the first case, medicinal products are often exposed to thermal variability beyond label claim without the support or documentation of allowable excursion data to justify the variability. Given that few distributors use electronic temperature monitoring devices calibrated to NIST standards and compliant with CGMP and USP <1118>, few can support their current processes.

In the second case, the distributor has very likely absorbed higher-than-necessary costs in an effort to maintain label claim during the later stages of distribution—arguably the most difficult to control.

If pharmaceutical manufacturers could get comfortable with a process to better manage allowable excursions in later stages of distribution, they could help increase compliance while ensuring patient safety.

LOOKING FORWARD

Johnson & Johnson's (J&J) Ortho Biotech division has deployed Sensitech's TagAlert electronic validated temperature indicator in each four-vial carton of Procrit (Epoetin Alfa) and has designated in the prescribing information that the device "will be triggered when exposed to temperatures below the recommended storage conditions of 2° to 8°C (36° to 46°F)." As a result, J&J has taken a proactive position to manage later stages of distribution by applying a validated electronic temperature indicator at the point of packaging. The indicator is designed to monitor the cumulative effects of storage conditions all the way to the patient and can be viewed through the packaging by supply-chain partners at any stage of distribution. While the alarm thresholds in the monitor are set outside the published label storage conditions, they are supported by the company's quality systems. Through this program, J&J has gone above and beyond what others in the industry have done by taking responsibility for ensuring product quality and patient safety across the entire supply chain.

Longer term, other manufacturers will likely take a similar approach of monitoring bulk shipments with temperature data loggers. They will want to have data that support their quality programs, while applying cost-effective validated electronic indicators at a more granular distribution level to ensure compliance with regulatory expectations and protecting patient safety. Alternatively, manufacturers and supply-chain partners may eventually elect to collectively manage some expanded temperature range for the distribution environment. In this case, increased monitoring in later stages of distribution would provide the necessary documentation required to manage expanded storage temperatures, as well as provide opportunities for costs-savings in the form of reduced packaging and distribution expenses. ■

1. USP <1079> Good Storage and Shipping Practices, U.S. Pharmacopeia (USP) 28, Suppl. (2) (November 1, 2005).

2. Holloway, I. "Understanding and Complying with MHRA Guidelines" Presentation—Pharma IQ's IPQC 8th Annual Cool Chain Europe Conference, Brussels—January 28, 2009.

3. Motta, R., "Cold Chain Management: Requirements and Recommendations" Presentation—Parenteral Drug Association (PDA) Pharmaceutical Cold Chain Interest Group (PCCIG) Conference, Bethesda, MD—March 13-14, 2008.

ABOUT THE AUTHOR

Henry Ames joined Sensitech in 2004 as the director of strategic marketing. He focuses on global market analysis and strategic marketing initiatives for the Life Science vertical.

Prior to Sensitech, he was a principal at Megunticook Management, a venture capital firm in Boston with $150 million under management and investments in promising communications, media and technology companies. While at Megunticook, Ames focused on supply chain-related investments. Before that he was manager of business development for Yantra, a leading provider of distributed order management and supply chain-fulfillment software.

Ames earned an MBA from the F.W. Olin Graduate School of Business at Babson College, and a double major in Business Management and Entrepreneurship from Florida State University. Ames also serves as a member of the Board of Overseers of the Beth Israel Deaconess Medical Center in Boston, MA.

Henry Ames
Director of Strategic Marketing, Sensitech
800 Cummings Center, Suite 258X
Beverly, MA 01982
Phone: 978-720-2541
Email: hames@sensitech.com

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