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Reconsidering Temperature Indicators

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By Henry Ames, Director of Strategic Marketing, Sensitech

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Time-temperature integrators (TTIs), commonly referred to as chemical indicators, are fairly popular, particularly for last-mile distribution. They change color or physical appearance after exposure to temperature variations over time. However, they are not supported by regulatory or standards-based guidance for good cold-chain management practices (GCCMP). This paper will review global regulatory and standards-based guidance for time and temperature recording devices, including guidelines from FDA, United States Pharmacopeia (USP), and the World Health Organization (WHO). Documented evidence will support the author's conclusion that chemical indicators are not appropriate for use in the pharmaceutical industry and that electronic temperature indicators should be considered the most appropriate alternative, particularly for last-mile distribution.

REGULATORY & STANDARDS-BASED GUIDANCE

In 1998, the U.S. Department of Health and Human Services and FDA's Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research drafted a guidance document that stresses the importance of ensuring drug efficacy: "Current good manufacturing practices regulations applicable to drug manufacturers (21 CFR 211.142) state that [...] procedures shall include instructions for the storage of drug products under appropriate conditions of temperature, humidity, and light so the identity, strength, quality, and purity of the drug products are not affected."

Further, "The regulation governing state licensing of wholesale prescription drug distributors (21 CFR 205.50 (c)) states that all prescription drugs shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements[...] The regulation also states that if no storage requirements are established for a prescription drug, the drug may be held at [controlled room temperature]... to help ensure that its identity, strength, quality, and purity are not adversely affected."¹

Based on audits from regulatory agencies evaluating documentation to support the practices outlined above, pharmaceutical and biologic manufacturers consider temperature data loggers and the systems used to manage information they collect as "critical components" of overall cold-chain management.²

Given the importance placed on the data collected by temperature and humidity data loggers, standards-based guidance recommends that temperature and humidity monitoring devices be validated and calibrated to NIST traceable standards.


In USP <1118> Monitoring Devices—Time, Temperature, and Humidity, the section on Validation of Temperature and Humidity Monitoring Devices states: "Thermometers and hygrometers, used to provide data about the temperature and humidity exposure of a product, must be suitable for their intended use. Specifically, they must be appropriately validated. Validation is a process that assures the user of the monitoring device that the device has been

tested prior to use either by the manufacturer or the user, to assess the measurement accuracy, measurement responsiveness, and time accuracy, where appropriate."³

In addition, USP <1079> Good Storage and Shipping Practices states: "Validated, available temperature- and/or humidity-monitoring technologies can be used to monitor the overall environmental effect on compendial articles during shipment and distribution."⁴ Furthermore, USP <1079> states: "All equipment used for recording, monitoring, and maintaining temperatures and humidity conditions should be calibrated on a regular basis. This calibration should be based on NIST or international standards (see Monitoring Devices—Time, Temperature, and Humidity <1118>)."

PROBLEM DEFINED

Several key characteristics of chemical indicators make them unsuitable for use in the life sciences market. Lack of validation, subjective interpretation of results, and varying accuracy of the devices call their use into question. Given that it is not possible to validate a chemical indicator, it is not recommended that this device be used to make product-quality—related decisions for pharmacopeial articles. The USP <1118> Monitoring Devices—Time, Temperature, and Humidity section on "Validation of Chemical-Based TTIs" states: "This type of device presents a problem for validation because testing the individual device causes its destruction. For this reason, calibration of individual chemical-based TTIs



against a NIST-traceable standard is not possible.”

It is acknowledged in guidance-based documentation that accuracy and precision of chemical indicators may vary widely. And, while TTIs may be less expensive than electronic indicators, they are subject to interpretation. For example, the USP <1118> Monitoring Devices—Time, Temperature, and Humidity, section on “Temperature Measurement Technologies” defines a chemical device as “a device based on a phase change or chemical reaction that occurs as a function of temperature. Examples include liquid crystals, waxes, and lacquers that change phase, and thereby their appearance, as a function of temperature. Such materials represent the least expensive form of temperature measurement, but they may be difficult to interpret [...]. Accuracy and precision vary widely among different types [...].”

Additionally, the USP <1118> Monitoring Devices—Time, Temperature, and Humidity, section “Time-Temperature Integrators,” states: “An important characteristic of chemical TTIs is the precision with which the endpoint can be determined. It is difficult to quantify an indication such as a gradual color change. Accuracy may also vary widely with the control and quality of the manufacturing process.”

TREND TOWARD MORE DETAILED EVALUATION OF COLD-CHAIN ENVIRONMENT

WHO, in consultation with the UNICEF Supply Division and a limited number of manufacturers and test labs, develops performance specifications and test procedures for cold-chain equipment in support of the Expanded Program on Immunization (EPI). In 2004, WHO began improving on its historical Product Information Sheet (PIS) program by implementing the Performance, Quality, Safety (PQS) program for EPI equipment and began drafting new specifications and test protocols for cold-chain products, syringes, and related equipment. While

the process was lengthy, the PQS program launched in January 2007.⁵ Documents covering chemical indicators are titled “Irreversible Freeze Indicator” and cover “Performance Specification” and “Independent Type-Testing Protocol.”

WHO PQS Performance Specification Section 4.2.2, covering “Performance Accuracy,” defines the accuracy requirement at “ ± 0.5 °C or better as 0 °C,” which is an increased accuracy specification from ± 1.0 °C in the earlier PIS document.⁶ While it is difficult to state definitively that no chemical indicator product will ever meet this accuracy requirement, the author is not aware of any chemical indicator with published accuracy specifications that meet the current PQS requirements. Conversely, some electronic temperature indicators on the market have published specifications meeting the accuracy requirements outlined.

A study published in September 2006 and sponsored by the Immunization Program, Bureau of General Communicable Diseases, Department of Disease Control by the Ministry of Public Health in Thailand further documents the shortcomings of chemical indicators. The study monitored shipments of vaccines on a total of 48 routes throughout Thailand. Each shipment was monitored with both an electronic data logger and a chemical indicator. The report states that: “In total, 29 Freeze Watch indicators registered freezing conditions. These indicators had 81% sensitivity and 73% specificity, and some discrepancies were noted between indications of freezing as provided by Freeze Watch activation and by the data logger.”⁷

Another major drawback to chemical indicators is their inability to accurately record and measure time. Section 4.2.5 “Mode of Operation” of the PQS Performance Specification document states: “The product is to be triggered by exposure to a temperature of -0.5 °C, ± 0.5 °C, for 60 minutes ± 5 minutes maximum.” Some chemical indicators list

specifications for time accuracy performance as a percentage of the “runout distance” — $\pm 9\%$ of the target distance is typical. The time accuracy is dependent on a constant temperature, an obvious and inherent drawback to chemical indicators. To illustrate, a short time exposure at a relatively high temperature will generally produce results similar to a longer exposure time at a lower temperature. While time measurement accuracy will vary from manufacturer to manufacturer, electronic temperature indicators are inherently more accurate. A further benefit is that manufacturers of electronic temperature indicators often publish or can make available time-measurement accuracy—something that is typically lacking with chemical indicators.

WHO’s position of increasing the accuracy requirements for these types of monitoring devices and the recent study by the Ministry of Public Health in Thailand, exemplifies an industry trend toward a more detailed evaluation and greater scrutiny of temperature-sensitive product during storage, handling, and distribution.

ADDITIONAL CHALLENGES TO USING CHEMICAL INDICATORS

Additional challenges to using chemical indicators include storage and handling requirements, environmental preconditioning, and shelf-life considerations. Given the fragile nature of chemical indicators, it is imperative that their handling and storage prior to use is managed carefully and documented. In addition, many chemical indicators require thermal preconditioning prior to use, which can lead to varying performance characteristics given preconditioning variability. Furthermore, Section 4.2.10 “Shelf Life” of the PQS Performance Specification document requires a “minimum [of] 3 years from the date of manufacture, inclusive of operational life.”⁶ While some chemical indicators available do have published specifications meeting this requirement, not all do. It is critical

to carefully evaluate shelf-life performance prior to procurement.

CONCLUSION

Pharmaceutical manufacturers should carefully weigh the strengths and weaknesses of electronic temperature indicators and chemical indicators. Regulatory and standards-based guidance documentation outlines expectations for the use of validated and calibrated temperature and humidity instruments used for recording, monitoring, and maintaining temperatures and humidity conditions for pharmaceutical products. Given that chemical indicators or TTIs cannot be validated and guidance-based documentation raises questions about the accuracy, consistency, and subjective interpretation of these devices, they are not supported by current GCCMP documentation. ■

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Sensitech provides cold-chain visibility solutions for food, pharmaceuticals, biologics, and industrial chemical markets.

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