The Changing Environment for Monitoring the "Last Mile" of the Pharmaceutical Supply Chain

Executive Summary

There are several key industry trends that support Sensitech's position on the use of chemical indicators in the life sciences segment.

THESE FOUR KEY TRENDS INCLUDE:

1. Expanding regulatory expectations for documentation to ensure product quality across all medicinal products—particularly those products that fall outside the standard "refrigerated" storage condition of 2–8 degrees Celsius—to include products in the controlled room temperature (CRT) category.
2. Increased demand for ensuring end-to-end supply chain controls for all products with a published label storage condition—i.e., more focus on the "last mile" and later-stages of drug distribution.
3. Relaxation of standards-based guidance and some regulatory positions around the general use of chemical indicators.
4. Recognition that chemical indicator technology has improved.

These changes warrant a review of the use of chemical indicator technology, as well as the various applications where chemical indicators can become critical components in a temperature monitoring program.

Overview

When celebrated economist John Maynard Keynes was criticized for changing his opinions over time, he responded by saying, “When the facts change, I change my mind. What do you do, sir?”

Similarly, as technologies change, successful companies adopt and adapt. Microsoft, known for its desktop software, has now embraced the cloud. Netflix, which built its business on delivery of DVDs, is now a leader in video streaming. Walmart, with its extensive brick-and-mortar infrastructure, embraced the Internet and online commerce.

So it is with the technology of the cold chain.

For decades, Sensitech has carefully evaluated the performance and use of chemical indicators, watching as they evolved from often unreliable devices used in food and industrial applications to acceptable tools for life science applications as a result of technological improvements.

This paper will provide specific examples that support the premise outlined in the four key trends above. Specific references will link previous documentation to changes in new or revised versions of relevant industry standards-based guidance.

Since the original publication of U.S. Pharmacopeia (USP) <1079> “Good Storage and Distribution Practices” on Nov. 1, 2005, the global regulatory and standards-based guidance for the storage, handling, and distribution of temperature-sensitive medical products has continued to evolve. The past nine years have seen revisions of USP <1079>; in fact, it is currently being updated for a third iteration as a component of USP <1083> “Good Distribution Practices” (GDP). Additionally, Health Canada’s GUI-0069 “Guidelines for Temperature Control of Drug Products during Storage and Transportation” has been published and revised, a recent revision to the outdated USP <1118> “Monitoring Devices—Time, Temperature, and Humidity” has been released, as have the World Health Organization’s (WHO) Annex 9 and the new European Union (EU)—European Commission “Guidelines on Good Distribution Practices of Medicinal Products for Human Use,” to name a few.

While there is consistency across these documents and their revisions regarding the use of calibrated, electronic-monitoring devices, there is new text that clearly outlines a general acceptance for the use of chemical indicators—a position that was nebulous in the earlier documents. A thoughtful evaluation of the current regulatory and standards-based guidance indicates an acknowledgment for application-specific solutions: different monitoring devices and form-factors associated with different device classes, which are applicable for different uses when monitoring pharmaceutical products. In other words, the increased scrutiny on both “last mile” distribution and a broadening of general monitoring expectations to include those products stored at controlled room temperature warrant the consideration of chemical indicators.

A Deeper Dive

Changing Regulatory Expectations

New regulations regarding environmental controls place equal emphasis on all drugs with a published label storage requirement. While the risk-based approach still applies, the expectation for a reasoned approach, supported by science, documenting the performance qualification (PQ) is applicable for all products with a label storage requirement. This has created a challenge for an industry that has historically focused on biologics stored at refrigerated conditions of 2–8 degrees Celsius, and expands the expectations for process documentation to a vast majority of the products available today; including those with CRT label claims. Products falling into this category encompass consumer product goods (CPG) like infant formula and over-the-counter (OTC) products such as neutraceuticals, eye drops and cough syrups, as well as a number of traditional, solid-dose form Rx products.

- The new EU GDPs Section 9.2 “Transportation” states: “The required storage conditions for medicinal products should be maintained during transportation within the defined limits as described by the manufacturers or on the outer packaging.”[i]
- USP <1079> states: “Good storage and distribution practices apply to all organizations and individuals involved in any aspect of the storage and distribution of all drug products...”[ii]
- Health Canada’s GUI-0069 document states: “These guidelines are intended to be applicable to all persons and companies involved in the storage and transportation of drug products. All persons and companies including fabricators, packagers/labelers, testers, distributors, importers, and wholesalers have the responsibility for ensuring that appropriate storage and transportation conditions are maintained from the point of manufacturing up to the delivery of the drug products to the final distribution point.”[iii]

These statements are comprehensive and intended to encompass all products ingested, injected, absorbed or metabolized by the body through all stages of the distribution process.

End-to-End Supply Chain Controls

The revision to USP <1079> “Environmental Management System—Temperature Monitoring” reiterates points made clear in the earlier publication, supporting the need to document environmental conditions for storage, handling and distribution from the manufacturer to the patient—from end-to-end across the complex pharmaceutical supply chain. The revision to USP <1079> continues to support this position. Specifically, the revision to USP <1079> states:

- “Environmental conditions are important parameters to consider in the storage and distribution of all drug products and may require monitoring depending on the requirements.”
- “...Environmental recorders or devices should be used to confirm that an acceptable range has been properly maintained during each stage in the supply chain.”
- “An appropriate number of temperature monitor(s) should be used with every distribution process unless another process has been put in place to ensure specified temperature ranges.”

U. S. Pharmacopeia is proposing a new series of GDP general chapters under USP <1083> Good Distribution Practices. This new series is being developed based on a review of existing chapters USP <1079> “Good Storage and Distribution Practices for Drug Products” and USP <1197> “Good Distribution Practices for Bulk Pharmaceutical Excipients,” as well as the previously proposed general chapter: USP <1083> “Good Distribution Practices—Supply Chain Integrity.” Due to the overlapping and complementary elements of these three documents, they are being combined into general chapters encompassing material flow beginning with initial procurement and continuing throughout the supply chain to the end user, and will include pharmaceutical components, products, medical devices and dietary supplements.

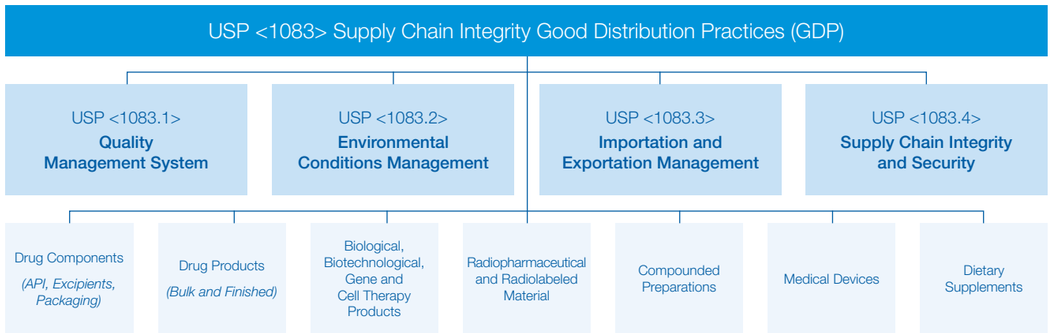

Exhibit 1[iv]

General Acceptance of the Use of Chemical Indicators

The Revision to USP <1079> "Distribution Management System, Validation and Thermal Performance Qualification for Transport Systems" originally published Dec. 1, 2012 states:

> Drug product transport systems should be continuously monitored by calibrated monitoring systems (continuous verification), or shipping systems should be qualified and based on historical data relative to the process. However, it may be acceptable to use product stability data and supply chain risk assessment to justify shipping without either continuous monitoring or qualification of the shipping system.[v]

The earlier version of USP <1079> published Nov. 1, 2005, focuses on the requirement for all equipment used to record, monitor and maintain temperature and humidity to be calibrated on a regular basis without mention of a qualified shipping system option.

This left the industry to interpret a more stringent approach toward the calibration of all devices. In fact, the earlier version of USP <1079> stated: "All equipment used for recording, monitoring, and maintaining temperature 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>)." The earlier 2004 version of USP <1118> further supported this position through the following text: "Thermometers and hygrometers... must be appropriately validated." This earlier version of <1118> went on to state: "...calibration of chemical-based TTIs against a NIST-traceable standard is not possible."

As a result of this analysis, the industry largely concluded that chemical indicator technology was not suitable for the pharmaceutical industry. Yet in 2004 the use of chemical indicator technology had already begun to find its way from the food industry to drug distribution through programs like those supported by the WHO.

Further supporting the change in sentiment regarding the suitability of chemical indicators for the life science segment, the 2012 revision to USP <1079> states: "Temperatures should be tracked using a monitoring system, and the monitoring devices used should be included in a calibration and/or preventive maintenance program. Environmental monitoring devices should be calibrated for their range of operation...

- "Electronic temperature monitors should be calibrated to National Institute of Standards and Technology (NIST) or other suitable standard...
- "Chemical temperature indicators may be used as appropriate."[vi]

The 2004 version of USP <1079> made no specific mention of chemical indicators, nor did it indicate an exception to allow for a lower standard of documentation regarding the performance of chemical indicators—i.e., calibration is not required.

In further support of these fundamental changes to industry standards, the Dec. 1, 2013 revision to USP <1118> states:

- "Electronic indicators require proper calibration. Single-use indicator performance can be qualified by the supply chain user by sampling and testing of multiple production lots...
- "It is acceptable to use the release test performed by the manufacturer of the indicator (based on the certificate of calibration or the certificate of analysis and the expiration date) in lieu of calibration or qualification...

These fundamental changes in U.S. Pharmacopeia's guidance regarding the suitability of chemical indicators are meaningful. That said, as with any guidance chapter, the ambiguity resides in the interpretation of the key words "as appropriate." It is Sensitech's belief that bulk shipments of medicinal product should still be monitored using calibrated instruments i.e., dataloggers—in the same way that a clear expectation exists for a calibration program during storage or "holding"[vii] of product.

There are a few other reasons for this position. First, high-value pallet and case-level shipments would likely warrant the use of a datalogger, in order to provide a quality department with a full time/temperature history of the environmental conditions experienced by the product. Should an excursion occur, this more detailed information may be used to justify further distribution or sale of the product based on a comparison against known stability data.

Second, to complete the point, Health Canada's GUI-0069 "Guidelines for Temperature Control of Drug Products During Storage and Transportation" states: "Temperature and humidity monitoring devices, such as data loggers, should be calibrated at predetermined intervals. Single use monitoring devices should be qualified (for example, verification of performance for indicator strips or freeze indicator units)."

Improvements in Chemical Indicator Technology

The original version of USP <1118> listed four general categories of chemical indicators or time temperature integrators (TTI)—types 1 through 4— including: "Chemical-Physical Based, Chemical Polymerization Based, Diffusion Based, and Enzyme Based."[viii] While the revision to USP <1118> is organized slightly differently, it includes all previous categories of devices and includes a new category that provides greater clarity around the different types of technologies, including those technologies that represent improvements over historical classes of devices.

The revised document highlights the point that chemical indicator technology can be considered for item-level applications and outlines two basic types of chemical indicators (1) a threshold indicator that responds to a specific temperature and (2) a TTI that responds to cumulative heat exposure.

While some of the historical challenges that have hindered the use of chemical indicators remain, a number of critical hurdles have been overcome.

CALIBRATION

As previously stated, while there remains an expectation for calibration of electronic temperature monitoring devices, single-use indicator performance may be qualified through sample testing of multiple production lots. Additionally, once a supplier has been successfully audited, it is considered acceptable to rely on the release test performed by the manufacturer, based on the Certificate of Calibration or Certificate of Analysis and the expiration date. The auditability of chemical indicator manufacturers has proven successful; testing and performance characteristics can be demonstrated at the batch-level.

SUBJECTIVE INTERPRETATION

While it depends on the type of technology considered, suppliers of new threshold chemical indicator technology have improved the clarity around the interpretation of the device. Some devices, for example, go from gray to black. Others offer a more intuitive and universal interpretation of a change from green to red. That said, traditional TTI technology tends to experience more challenges when it comes to interpretation of the unit. In fact, the revision to USP <1118> states: "The accuracy and precision of these indicators depend, to some extent, on human interpretation." USP <1118> further points out: "An important characteristic of chemical based TTIs is the precision with which an endpoint can be determined."

ACCURACY

There are three commonly referenced accuracy specifications: temperature accuracy, time accuracy, and measurement responsiveness. The measurement accuracy text outlined in the revision to USP <1118> did not change significantly. The revision describes measurement accuracy as referring to the "closeness of the value obtained with a particular device and the true value of the object or environment under measurement." In general, temperature-accuracy specifications have improved for specific classes of chemical indicators, namely threshold indicators. New technologies enable suppliers to modify or even tighten the accuracy specification based on unique customer needs. However, in some cases, tighter accuracies may result in a shorter shelf life for the indicator; these factors should be evaluated carefully. The time-accuracy specification for USP <1118> did not change between the earlier and revised version of the document. The time-accuracy specification states: "...time accuracy is expressed as a +/- percentage of total duration of the recording period. For pharmaceutical applications, a +/- 0.5% time accuracy is adequate." For TTI technology, the time-accuracy specification tends to be a challenge because by definition it is dependent on a constant temperature, an obvious and inherent drawback to the technology. When a time-accuracy specification is provided by a manufacturer, it tends to be vague—i.e., for the "Chemical-Physical Time-Temperature Indicators" a percentage of the "run out distance" of the unit may be quoted. Conversely, time-accuracy specifications are often provided for threshold technology since they can be tested and reported against. The accuracy specification for measurement responsiveness was essentially eliminated in the revision to USP <1118>. The earlier version defined measurement responsiveness as the "time, t½, required for a device to read a value of (x + y)/2 after an instantaneous change in the property being measured from x to y. Measurement responsiveness is typically defined for the operating range of a device." The revision only includes this last sentence: "Measurement responsiveness typically is defined in a device's specifications for its operating range." In the absence of any new standard, the industry continues to revert back to the original standard outlined in the earlier version of USP <1118>. Given the small form factor and minimal thermal mass of chemical indicator technology, the response rate or time for equilibration of these types of devices tends to be quite rapid meeting the outlined performance specification. That said, it should be noted that some devices require an extended time frame upon receipt to allow the unit to "trigger" or provide a visual indication before the unit can be interrogated by the user.

A number of historical challenges have been overcome completely or addressed in a more effective manner. Examples of issues worthy of evaluation include shelf life, storage and handling requirements, environmental pre-conditioning / post-conditioning, shipping requirements and deployment challenges, i.e., the need to physically start or apply the unit.

Conclusion

Thomas J. Watson, Sr. CEO of IBM from 1914 to 1956 was often quoted stating: "Analyze the past, consider the present, and visualize the future."[ix] To continue to meet and exceed customer expectations, an organization needs to remain diligent in its analysis of changing segment dynamics. In looking at the changing expectations for the storage, handling and distribution of medicinal products, it is clear that there is greater emphasis placed on all products with a published label storage condition, including broad classes of consumer and OTC products that have not historically been monitored. Additionally, there is an increased concern for maintaining proper environmental conditions during later stages of drug distribution. Lastly, there is a clear and recent change regarding the acceptance of chemical indicator technology in the life sciences vertical, as well as an acknowledgment of meaningful advancements in the performance of this class of devices. As companies look to expand their quality management systems to ensure product quality and patient / customer safety, the application of chemical indicators for last-mile monitoring programs should be explored.

[i] European Commission, Guidelines of 5 November 2013 on Good Distribution Practices of Medicinal Products for Human Use (2013 3/C 343/01)

[ii] USP General Chapter <1079> "Good Storage and Distribution Practices" 2013, USP 36, NF 31, p. 3 Scope

[iii] Health Canada Guide 0069, "Guidelines for Temperature Control of Drug Products During Storage and Transportation," January 28, 2011

[iv] USP Chapter <1083> Good Distribution Practices, PF 38(2) [Mar-Apr 2012] / Briefing USP <1083> subsequently cancelled – revision comments due May 2014 (GCPS: D.G. Hunt.) Correspondence Number – C139772

[v] USP General Chapter <1079> "Good Storage and Distribution Practices" 2013 USP 36, NF 31, p.12 Distribution Management System

[vi] USP General Chapter <1079> "Good Storage and Distribution Practices" 2013, NF 31, p. 13 Environmental Management System

[vii] To support the quotation of the words "as appropriate" – USP General Chapter <1079> "Good Storage and Distribution Practices" 2013, NF 31, p. 13 Environmental Management System; to support the quotation of the term "holding" and reference to the CFR: U.S. Federal Food and Drug Cosmetic Act Chapter V section 501, sub-chapter A, (2)(b)

[viii] USP General Guidance Chapter <1118> "Monitoring Devices - Time, Temperature, and Humidity," USP 27, 2004

[ix] Quintessential Quotes, IBM Corporate Archives, Thomas J. Watson, Sr. (http://www-03.ibm.com/ibm/history/documents/pdf/quotes.pdf)

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