The United States Pharmacopeia and The National Formulary (USP–NF) contains definitions, tests, and standards in its monographs for chemical and biological drug substances, dosages and compounds, excipients, medical devices and dietary supplements. The General Notices and Requirements section of the United States Pharmacopeia (USP) and the National Formulary is often updated and revision numbers are represented as USP 33-NF 28, signifying the thirty-third revision and the twenty-eighth edition. General Notices and Requirements contains several supplemental assumptions, definitions, and default conditions for the interpretation and application of the official articles. There are five general chapters that touch upon the temperature-sensitive supply chain:

- **USP General Chapter <1079> “Good Storage and Shipping Practices”**
- **USP General Chapter <1083> “Good Distribution Practices—Supply Chain Integrity”**
- **USP General Chapter <1118> “Monitoring Devices time, temperature and humidity”**
- **USP General Chapter <1077> “Good Packaging practices”**
- **USP General Chapter <1150> Pharmaceutical Stability**

The published standards of USP represent scientifically sound criteria that can be used to compose justifications for exceptions and qualifications of processes. Under USP General Chapter <1079> there is a graphic of a typical Drug Product Distribution process that shows several different paths a drug can take from its “Innovator/Generic Manufacturer” to the patient. The shortest path is a sample distribution that can go from the original manufacturer via a dispensing doctor to a patient: 3 steps. A longer (and more typical) path can take the drug from its original manufacturer, to a re-packager, to a distributor, back to a packager on to a pharmacy, hospital, governmental agency, clinic etc., and finally to a doctor who dispenses to a patient.

In 2011, the USP Pharmacopeial forum proposed a new general information chapter <1083> “Good Distribution Practices – Supply Chain Integrity” in order to create a more comprehensive standard. This proposed general chapter contains quality standards for drugs and drug ingredients in the U.S. The proposed standard covers: importation, counterfeit drugs and medical devices, best practices to combat counterfeit drugs and medical devices, and diversion and theft. As of this writing, the committee revising this chapter is still in discussion with plans to complete and publish in Pharmacopeial Forum (PF) 38(2) in the spring of 2013.

The USP General Chapter <1079> Good Storage and Distribution Practices recommends cold-chain management to ensure that the necessary shipping conditions are maintained during distribution, noting that extreme temperatures should be avoided. The monograph refers to 21 CFR Parts 203 and 205 as the regulations outlining “several legs” of the distribution chain for prescription drugs. Both manufacturers and distributors are responsible for establishing and maintaining proper product shipping. The section “Distribution and Shipment of Pharmacopeial Articles” recommends using the following items as qualifying information on the cold chain:

- ICH stability studies
- Temperature cycling studies
- Stability shipping studies
- Ongoing regulatory stability commitment studies
- Market experience portfolio (i.e., product complaint files, historical product performance data, product development data)
- Product labeling commitments
For dealing with high variability within shipping and distribution applications, USP<1079> contains a section titled “Physical Challenges” that mentions accepted testing methods for assessing a cold chain: “Standard Practice for Performance Testing of Shipping Containers and Systems” (ASTM D4169-98), and the International Safe Transit Association’s (ISTA) test procedures.

For maintaining appropriate storage conditions, a temperature profiling study is recommended to establish a profile and qualify storage equipment. Here we see where the FDA and USP overlap, so we should clearly outline what the relationship between those organizations is. While the USP is an independent organization authorized by U.S. law and is concerned mostly with dosage forms; it is not a governmental agency of enforcement, as is the FDA.

The USP sets standards for tests and drug chemistry, as well as strength and formulation, and publishes these items to U.S. market stakeholders, including drug manufacturers, drug distributors and the current drug enforcement agency in the U.S. – the FDA.

Both organizations share the goal of ensuring that drugs are not adulterated in any way; however, the FDA has jurisdiction over the drug development process (i.e.: clinical trials, NDAs, etc.). The USP lists and describes products that have been produced in a compendium, updating that product’s information as it becomes available and until it is no longer produced.

As part of its cold-chain management recommendations, USP <1079> describes the following guidelines:

- Shippers/Distributors must follow manufacturers’ storage specifications that are on the label.
- Manufacturers should attach monitoring and recording devices to product OR ship under controlled, monitored and recorded conditions.
- Operational and Performance Qualification testing should reflect load and expected environmental extremes using an established protocol.
- Basic packaging principles for protecting contents will be tested and used – ensuring that temperature profiles are performance qualified.
- Temperature cycling studies to determine the effects of short-term excursions should be performed.
- Containers should be tested using ASTM and/or ISTA testing methods.
- Pharmaceuticals must be transferred to controlled storage conditions within two hours of receipt at a distribution center.

The USP 26 states that if there are no specific storage parameters within a monograph, “An article for which storage at controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.” However, any stability data on the label should apply and if there is no such data, the item must be protected from moisture, freezing, and excessive heat by whatever means are necessary.

In conclusion, the standards outlined in the USP NF chapters on storage and shipping, supply chain integrity and other cold chain management issues provide recommendations on what data will determine a product’s shipping criteria. It is helpful to think of the USP chapters that touch upon cold chain as a lens through which you view your product’s transport process. Combined with product monographs, the chapters provide a solid basis in Good Distribution Practice for your cold chain applications.

For more information on cold chain solutions, contact your local Vaisala representative, accessible here: www.vaisala.com/lifescience

Sources

1. See USP <1079> “Distribution and Shipment of Pharmacopeial Articles” Figure 1, “Drug Product Distribution”


4. USP <1079> “Distribution and Shipment of Pharmacopeial Articles” Retrieved 5/28/2012