

The Fifth Element of Authentication: Condition

Monitoring Temperatures of Cold Chain Drugs Ensure Efficacy, Safety and Brand Integrity

Counterfeit Cold Chain Drugs

While the worldwide pharmaceutical market is in excess of \$400 billion, the U.S. pharmaceutical market is valued at greater than \$200 billion and includes about 14,000 drugs.¹ To reduce the costs of producing these drugs, U.S. manufacturers are going abroad. However, this raises counterfeit concerns. According to Physician's News Digest, "as drug manufacturers have moved their production plants worldwide, some countries like Pakistan, India, Thailand and Mexico have become havens for the production of unapproved, knock-off drugs."²

The cold chain pharmaceutical market is about \$44 billion and growing much faster than the traditional non-temperature sensitive drugs.³ Cold chain is an increasingly important component of the overall global pharmaceutical supply chain. Besides an increased number of investigational new drugs (INDs) in clinical trials and increased investment in research and development (R&D), the compound annual growth rate (CAGR) for cold chain pharmaceuticals has been roughly 21 percent for the past five years.⁴

Of the top 32 drugs that are counterfeited the most, more than 50 percent of them have strict cold chain requirements, according to Florida's Bureau of Statewide Pharmaceutical Services and Drug Wholesaler Advisory Council. However, all of the top 32 most commonly counterfeit drugs have some cold chain requirement.

Cold chain drugs are most commonly counterfeited due to their high dollar value and physical characteristics. Biologic based pharmaceuticals do not face the same pricing pressure of traditional chemical based drugs because generic biologics have yet to be approved. According to In-PharmaTechnologist.com, "There is no approval process for biologics not cleared for market under the NDA [New Drug Application] process. In addition, it is not clear how much testing will be needed for drugs claiming to be comparable biologics."⁵ Also, because many cold chain pharmaceuticals come in liquid form, counterfeiters can easily dilute them with water. Also, temperature-sensitive drugs are expensive because there are no generic biologic equivalents.

Defining 'Authentication'

The definition of drug authentication, according to the Healthcare and Life Sciences Business Action Group (HLS BAG), is the process of determining whether something is what it is declared to be. HLS BAG is a division of EPCglobal Inc., which is committed to standards-based global supply chain solutions.

Authentication should answer the following questions:

- Does the packaging accurately represent the product contained inside?
- Do the pharmacopeial properties listed on the label match the properties of the drug contained within?
- Has the drug's handling, storage and distribution environment been maintained within Food and Drug Administration (FDA)-approved storage conditions, printed on the labeling of the product, at each stage and destination of the supply chain?

Some new pedigree laws include authentication and storage condition clauses aimed at protecting patient safety. For instance, according to a February 2005 news release, “Under a recent Florida law advanced by Attorney General Crist, a drug cannot be legally sold in Florida without a valid pedigree guaranteeing that it is **authentic and has been properly stored**.”⁶ In the news release, Florida Attorney General Charlie Crist highlighted an illegal interstate prescription drug operation with purchases totaling more than \$1.2 million.

Anti-Counterfeit Methods

According to an FDA 2004 report (“Combating Counterfeit Drugs: A Report of the Food and Drug Administration”), authentication technologies serve two purposes:

1. “They make it more difficult and expensive to produce a copy of the drug or its packaging and labeling.
2. “They provide a means for determining if a specific drug, package or label is authentic.”⁷

Currently there are four methods of determining if a product is genuine. Some of these product authentication strategies were first introduced by the FDA in its 2003 counterfeit drug task force report⁸, which was updated in 2004: “Combating Counterfeit Drugs: A Report of the Food and Drug Administration.”

The following first two authentication strategies focus on package security and brand protection of manufacturers. The other two relate to diversion.

- **Overt:** Involves forms of packaging elements that are visible to the naked eye. Some examples include holograms, color-shifting inks, decorative fonts, specific types of watermarks and guilloche—elaborate borders that are also often found on currency.
- **Covert:** Uses forms of packaging elements that are incorporated into the product and not visible to the naked eye and requires special equipment for visualization. Some examples include specific types of watermarks or invisible inks that are detected only under ultraviolet or other fluorescent light as well as invisible bar codes, which require specific readers.
- **Forensic:** Includes chemical markers and taggants, which require sophisticated analytical equipment often found in a forensics lab. These detection methods are often used when diversion is suspected. Also, the product may need to be destroyed to conduct an assay of its ingredients as well as retrieve the specific detection form.
- **Logical:** Relies on track and trace technologies to determine if the right product followed the right distribution path. Logical encompasses product serialization to determine who is responsible for diverting the product or if it were sold into the right channel. Many pedigree solutions incorporate the logical method of authentication.

A program designed to protect the authenticity and quality of a drug as it flows through the pharmaceutical supply chain needs to incorporate multiple technologies and methods to have a major impact.

However, some manufacturers have focused much of their efforts on the quick-to-implement overt and covert strategies. According to HLS BAG, “overt and covert packaging technologies are rendered useless if a drug product is repackaged, a practice that is common in the industry and subject to only minimal regulation.”⁹

Because the forensic attribute is more difficult to implement, it is by nature more costly to deploy. Additionally, conducting these tests can be time-consuming. Furthermore, some of the product's shipment is destroyed for testing purposes.

Condition: An Essential Component of Any Authentication Program

None of the aforementioned methods address the adulteration of cold chain drugs as a result of temperature abuse. Manufacturers and distributors following Good Cold Chain Management Practices™ practices routinely monitor product temperatures while the products are in their possession. Temperature is an element of condition along with light, shock, vibration and humidity.

Yet, the supply chain is inherently complex with its many supply chain partners: manufacturers, distributors, third-party packagers, primary and secondary wholesalers, retail and online pharmacies, hospitals and clinics. Because of the various exchange and drop-off points, distribution environments often involve several modes of transportation, climate zones and seasonal changes. Drug shipments can experience vast temperature swings while sitting on a warm, open-air dock, waiting to be loaded; or while resting in an overcooled cargo-hold of a plane, waiting to be unloaded.

A drug shipment from a European warehouse to a European investigational site is expected to change hands nine times and be exposed to as many temperature fluctuations.¹⁰ The transit time from East European countries to some Latin American countries may take up to a week or more.¹¹ To compound the issue, drug shipments are facing lengthy clearance procedures at customs. Some international drug shipments may take two weeks or more to receive clearance, raising the concern that the cargos are not always in their proper controlled temperatures.

The pharmaceutical supply chain must consider all these factors. Thus, a fifth authentication method that needs to be addressed is condition in order to not only ensure a product's identity but also its quality.

Several regulatory guidance documents link quality and authentication. In 1998, the U.S. Department of Health and Human Services, the FDA, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research drafted a guidance document focusing on the "Stability Testing of Drug Substances and Drug Products." They used the term "identity" to describe authentication and stressed the importance of product identity and quality relating to proper storage environment. Below are some excerpts from the document that illustrate this point:

"Current good manufacturing practices (CGMP) 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."¹²

"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."¹³

The United States Pharmacopeia issued in November 2005 General Chapter <1079> “Good Storage and Shipping Practices.” This guidance document is geared toward manufacturers, distributors, wholesalers, repackagers and transport logistics providers. The overall goal of the updated chapter is to establish storage, handling and distribution standards that will ensure a product’s “**identity, strength, quality, and purity**” across the entire distribution channel.¹⁴

Cold Chain Drugs, Adulteration and Quality

The FDA explicitly states that improper “holding” environments, which include adequate temperature settings, can cause a drug to become adulterated, resulting in poor product quality. Below is one highlight from the “Stability Testing of Drug Substances and Drug Products” report:

“Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act states that a drug shall be deemed to be **adulterated** if the facilities or controls used for **holding drugs do not conform to or are not operated or administered in conformity with good manufacturing practice** to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the **quality** and purity characteristics, which they purport or are represented to possess.”¹⁵

Cold chain drugs are vulnerable to improper temperatures—which can go well beyond a manufacturer’s published storage requirements—during the distribution process, thereby impacting their condition and efficacy. And, not knowing the bona-fide condition of a drug can be harmful to a patient and damage a manufacturer’s brand by being susceptible to lawsuits and public relations problems. Obviously, these issues have a significant financial impact that could negatively influence shareholder and investor confidence.

Temperature Abuse and Patient Safety

A drug that has been temperature abused is every bit as dangerous as one that is not authentic. For instance, therapeutic proteins, which are used in cancer therapy, cosmetic reconstruction and some chronic disease treatments, require special care because temperature fluctuations can cause these drugs to be harmful to the patient. “Degraded proteins tend to aggregate and also can assume other unnatural chemical states. These unnatural states tend to activate the body’s immune system, potentially creating an immune response against the therapeutic protein. Such antibodies can act to neutralize the effect of the therapeutic protein, or worse, act to neutralize the effect of the body’s own naturally occurring hormones. In these cases the degraded form of the drug can prove to be potentially harmful.”¹⁶

Liquid drugs, especially insulins, that undergo quick freeze-thaw cycles often pose serious quality concerns, resulting in product efficacy issues. Some solid dosages also have a negative impact when exposed to freezing temperatures. “For example, freezing will cause modified insulins (i.e., those containing a precipitate such as NPH insulin, Ultralente® insulin, or Lente® insulin) to re-suspend improperly after thawing, reducing accuracy of dosing. For modified release solid oral dosage forms there is concern that freezing may alter the drug products dissolution properties.”¹⁷

Conclusions

The counterfeiting of cold chain drugs has become a major concern for manufacturers, their supply chain partners as well as regulators. Extra measures—including new techniques, processes and systems—must be

taken to ensure the pharmaceuticals' quality and integrity as well as maximize patient safety and protect manufacturers' brand equity.

According to the FDA "Combating Counterfeit Drugs" report, there is "the need for development of secure business practices by all stakeholders in the drug distribution chain because each stakeholder has a responsibility to ensure that pharmaceutical products are **authentic**."¹⁸ Stakeholders range from manufacturers and distributors to primary and secondary wholesalers.

Because the pharmaceutical supply chain is immensely complex, cold chain drugs are inherently susceptible to temperature excursions. By implementing a comprehensive temperature monitoring program as part of Good Cold Chain Management Practices, only then can manufacturers ensure their products' condition, quality and original identity as cold chain products move from one stakeholder to another.

While there are currently four methods for drug authentication, condition is an additional requirement that has been overlooked by manufacturers and the industry at large, causing safety issues and weaknesses in the U.S. pharmaceutical supply chain. A product that has been diluted by a counterfeiter is just as dangerous as a product that has been temperature abused.

According to the FDA: "The best strategy is to use multiple, periodically changing, **authentication measures** on a product-specific basis after doing a risk analysis that takes into account the risk that the product will be counterfeited and the public health risk if the product is counterfeited."¹⁹

About Sensitech Inc.

Sensitech is the leading provider of cold chain visibility solutions that enable global leaders in Food and Pharmaceuticals to track and monitor assets across the supply chain, protecting the integrity of their temperature-sensitive products. Our product portfolio includes comprehensive analytic services, enterprise software systems and validated data acquisition devices. The company is based in Beverly, Massachusetts, and has offices in Amsterdam, Calgary, Melbourne, Redmond and Santiago with service and distribution offices around the world. For additional information about Sensitech, call 978-927-7033 or visit www.sensitech.com.

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