



Authentication From a Cold Chain Perspective

Manufacturers, distributors and their supply chain partners should include product condition or, more broadly, product quality, as part of their product quality program

THE PHARMACEUTICAL SUPPLY CHAIN is undergoing intensive re-evaluation because of issues involving counterfeiting, pedigree rules, and brand protection. Product safety measures such as covert or overt authentication, and RFID tagging, are being offered as responses to these issues. At the same time, cold chain management—the control, monitoring, documentation, and analysis of temperature data—is rising in importance. The volume of temperature-sensitive products, especially biological-based products, is increasing dramatically. More drugs are moving internationally at multiple stages of the products' supply chain. In addition, a host of new cold chain regulatory and guidance-based documents have been published in the past twelve months.

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MANY INDUSTRY REPRESENTATIVES view creating a safe and secure supply chain and ensuring product quality as two separate issues. Creating a safe and secure supply chain is typically linked to drug pedigree requirements and thwarting counterfeiting. On the other hand, ensuring that a product's quality has not been compromised is most closely linked with protecting the cold chain. Separate regulatory requirements and separate operational processes compound the lack of congruence between these two topics.

It is our contention that the better course of action is to incorporate both product quality and authentication into a comprehensive product-quality system. There are

technical reasons for doing this—mostly involving the regulatory perspective of “adulteration” as detailed in FDA cGMP rules. But, the broader rationale is that it makes sense to manage authentication as one of several factors influencing overall product quality. The reality is that a product that is temperature-abused is just as dangerous as one that is not genuine.

Manufacturers, distributors and other supply chain partners following Good Cold Chain Management Practices (GCCMP) routinely monitor product temperatures while the products are in their care. Yet, product quality or the documentation of environmental conditions remains largely omitted from discussions focused on developing a safe and secure supply chain.

By implementing a comprehensive

temperature monitoring and documentation program as part of an overall product quality initiative—which would include anti-counterfeit, only then can pharmaceutical manufacturers ensure their products' condition, quality and original identity as cold chain products move from one stakeholder to another.

The correlation between cold chain drugs and counterfeiting

Today's debate over pedigree rules are directed mostly at illicit diversions and counterfeiting. However, cold chain considerations are also a factor. For example, of the top 34 drugs that are of most concern for counterfeiting according to Florida's Bureau of Statewide Pharmaceutical Services and Drug Wholesaler Advisory Council, more than 61% have strict cold-chain requirements (2-8 degrees Celsius, store frozen, do not freeze). [1] However, 100% of that list has some thermal requirements. (Even the solid-dose oral products on the list require maintaining Controlled Room Temperature during shipment and storage.)

Cold chain drugs are most commonly counterfeited due to their high dollar value and physical characteristics. Biologic-based pharmaceuticals are expensive both because

of manufacturing complexity and the lack of generic equivalents. In addition, many cold chain pharmaceuticals come in liquid form, providing opportunities for adulteration.

For the foreseeable future, this overlap is only going to get worse, because biological products are a high-growth segment of the pharmaceutical market. IMS Health (Fairfield, CT) reported a \$52.7-billion global market for 2005, up 17.1% from the year before). [2] The overall market grew 7.1% in 2005, to \$602 billion. Cold chain products represent a high-value, high-growth segment of the worldwide pharmaceutical market.

Defining 'authentication'

According to members of the Healthcare and Life Science Business Action Group (HLS BAG), a division of EPCglobal committed to standards-based global supply chain solutions, drug authentication is the process of determining whether something is what it is declared to be. While this description makes perfect sense, ultimately, authentication should answer the following questions:

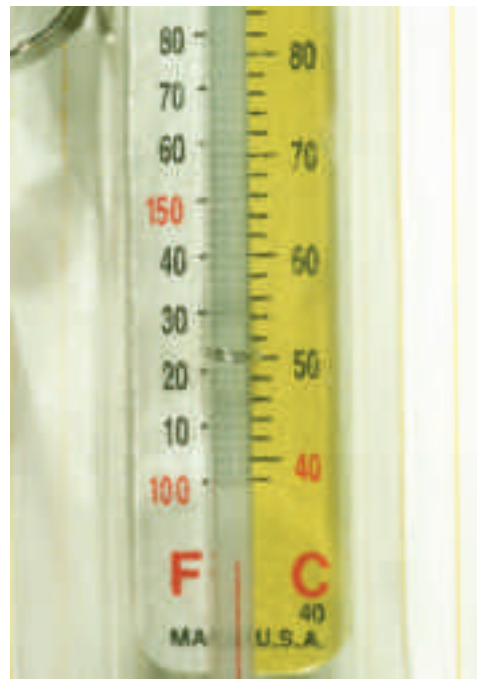
- Does the packaging accurately represent the product contained inside?
- Do the pharmacopeial properties listed on the label match the properties of the drug contained within?
- Has the drug's handling, storage and distribution environment been maintained within Food and Drug Administration (FDA)-approved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

While the expectations are not entirely clear, some new pedigree documentation includes authentication and storage condition clauses aimed at protecting product quality. For example, according to a February 2005 news release, "Under a recent Florida law advanced by Florida Attorney

General Charlie Crist, a drug cannot be legally sold in Florida without a valid pedigree guaranteeing that it is authentic and has been properly stored." [3]

Methodologies for thwarting counterfeiters

According to FDA, authentication technologies serve two purposes: creating obstacles for easy reproduction; and providing



means of authenticating legitimate product. [4] FDA has identified four general principles of protecting the authenticity of products: overt and covert identification (special inks or printing on packaging); forensic (chemical markers and taggants detectable with lab equipment), and logical (track and trace programs). While it is understood that in isolation, none of the four current methodologies solve the counterfeiting problem in its entirety, it is important to note that even collectively these elements fail to protect patient safety because they are missing the remaining essential component: condition.

Product condition elements

Temperature is the primary element of

condition along with light, shock, vibration and humidity that can affect product quality. And, because the pharmaceutical supply chain is inherently complex, there are many opportunities for condition to negatively affect the quality of a product prior to dispensing the product to the patient. The pharmaceutical supply chain incorporates many 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. As a result, drug shipments can experience significant temperature swings throughout this complex distribution model.

For example, according to one reference, a drug shipment from a European warehouse to a European investigational site can change hands nine times and be exposed to as many temperature fluctuations. [5] The transit time from East European countries to some Latin American countries may take up to a week or more. 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 cargo is not maintained at its proper controlled temperature.

To support a safe and secure supply chain and ensure patient safety, the pharmaceutical industry, in conjunction with regulatory and standards-based organizations, should consider all distribution channel variables including not only diversion but also environmental conditions.

Several regulatory and standards-based 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.” This document stresses the importance of condition and its ability to negatively affect a product’s identity, strength, quality, and purity. Below are some excerpts from the document [6] 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.”

“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.”

In November 2005, The United States Pharmacopeia (USP) issued 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 document is to establish storage, handling and distribution standards that will ensure a product’s “identity, strength, quality, and purity” across the entire distribution channel. [7]

A temperature-abused product is an adulterated product

The FDA explicitly states that improper “holding” environments can cause a drug to become adulterated, resulting in poor product quality. Below, is a highlight from the

Direct Correlation Between Cold Chain and Authentication		
DRUG	COMPANY	COLD CHAIN REQUIREMENTS
Bextra	Pfizer	Store CRT (15°C – 30°C)
Celebrex	Pfizer	Store at 25°C; excursions permitted between 15-30°C
Combivir	GlaxoSmithKline	Store between (2° C - 30° C)
Crixivan	Merck	15° C - 30° C (room temp)
Diflucan	Pfizer	5° C - 30° C (do not freeze)
Epivir	GlaxoSmithKline	Store Below 25° C
Epogen	Amgen	2° C - 8° C
Gamimune	Bayer	Store in Refrigerator (do not freeze)
Gammagard	Baxter	Do not Exceed 25° C (do not freeze)
Immune Globulin	Telecris Therapeutics	Store 2° C - 8° C (do not freeze)
Lamisil	Novartis	Store below 25° C (away from heat)
Lipitor	Pfizer	CRT 20° C - 25° C
Lupron	TAP Pharmaceuticals	Store below 25° C (do not freeze, protect from light)
Neupogen	Amgen	Store 2° C - 8° C (avoid shaking)
Nutropin AQ	Genetech	Store 2° C - 8° C (avoid freezing)
Panglobulin	ZLB Bioplasma	Store at 15° C - 30° C CRT
Procrit	Ortho Biotech	Store 2° C - 8° C (avoid shaking)
Retrovir	GlaxoSmithKline	Store 2° C - 8°
Risperdal	Janssen	Store 2° C - 8° C
Rocephin	Roche	Store Frozen (below 20° C)
Serostim	Serano	Store Room Temp 15° C - 30° C (do not freeze)
Sustiva	Bristol Meyers Squibb	Store CRT 15° C - 30° C
Trizivir	GlaxoSmithKline	Store at 25° C (77° F); excursions permitted bet. 15° - 30° C
Venoglobulin	Alpha Therapeutic Corp.	Store at or below 25° C (avoid freezing)
Viagra	Pfizer	Store CRT 15° C - 30° C
Videx	Bristol Meyers Squibb	After mixing, store 2° C - 8° C
Viracept	Pfizer	Store 15° - 30° C (59° - 86° F)
Viramune	Boehringer Ingelheim	Store at 25° C (77° F); excursions permitted to 15° - 30° C
Zerit	Bristol Meyers Squibb	After mixing, store 2° C - 8° C
Ziagen	GlaxoSmithKline	Store at CRT 20° C - 25° C (do not freeze, may be refrigerated)
Zocor	Merck	Store 5° C -30° C (away from light and moisture)
Zofran	GlaxoSmithKline	Store 2° C - 30° C (protect from light, excessive heat and freezing)
Zoladex	AstraZeneca	Store at room temperature (do not exceed 25° C)
Zyprexa	Eli Lilly	Store CRT 20° C - 25° C (MKT not more than 25° C)

Of 34 pharmaceuticals named on the “Florida List,” of high counterfeit potential, 21, or 61%, have specific temperature limits (2-8° C, ‘store frozen,’ ‘do not freeze’)

“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.”[8]

Cold chain drugs are vulnerable to temperature abuse during the distribution process, thereby impacting their condition and efficacy. Without documentation to ensure the quality of a drug, the current drive for a safe and secure pharmaceutical supply chain is falling far short of its intended goal.

Temperature abuse negatively affects patient safety. 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. . . . In these cases the degraded form of the drug can prove to be potentially harmful.” [9] The American Diabetes Association has warned against the problems of improperly freezing and then thawing modified-release, solid oral dosage form; freezing may alter the dissolution properties of the product. [10]

Unifying product safety oversight

Pharmaceutical manufacturers and distributors have mechanisms in place both to address counterfeiting issues and to monitor product condition. It makes sense, then, to unify these mechanisms into a comprehensive temperature-monitoring and docu-

mentation program as part of an overall anti-counterfeit initiative. Only then can manufacturers ensure their products’ condition, quality, efficacy and original identity as they move from one stakeholder to another.

Good Cold Chain Management incorporates proper packaging materials to maintain a desired temperature while product is in transit, and a comprehensive cold-chain data-collection and information-management system to document and evaluate product condition. Evolving authentication systems depend on both physical features of the drug package and an IT system to record specific security features for later verification. We suggest that manufacturers and distributors should have the cross-functional communications in place so that both condition and authenticity are properly monitored.

When working to ensure a safe and secure supply chain, it is critical to remember—a product that has been temperature-abused is just as dangerous as a product that is not genuine. **PC**

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Sensitech is the world’s leading provider of cold chain visibility solutions enabling global leaders in Food, Pharmaceuticals, Biologic and Industrial Chemical Markets to track and monitor assets across the supply chain, protecting the integrity of their temperature-sensitive products. For additional information about Sensitech, call 978-927-7033 or visit www.sensitech.com.



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