Cold Chain Compliance: Strengthening the Weakest Link

by James R. Darnell, Jr.
Managing Consultant

Tunnell
STRONGER PERFORMANCE AHEAD

From 2007 to 2008 the biotechnology industry experienced a year-to-year average growth rate of 19% and continues to grow rapidly. Today's global biopharma cold chain market is $5.1 billion and is expected to grow to $6.6 billion by 2011[1]. In the cold chain distribution arena, temperature-sensitive drugs such as biologicals make up approximately 10% of the roughly $200 billion pharmaceutical distribution industry, which includes trucking, air transport, warehousing, and delivery.

Given the extraordinarily high growth rate in the biopharma sector, commercial products on the market, the large number of products in clinical stages, and products approaching commercialization, regulatory agencies are focusing on evaluating life science companies and their cold chain compliance practices.

Cold chain failures have resulted in actions including litigation, product withdrawals, postponement of clinical trials, delays in product getting to the market, lost contracts, costly recalls, waste of product, and damage to reputation.

With so much at risk, both in the financial and patient safety realms, biotech companies, both emerging and established, must ensure that their cold chain management programs are sound and that the safety and efficacy of their products are sustained throughout the entire cold chain.

The Weakest Link

Currently, there are more than 400 biotech drug products and vaccines in clinical trials targeting more than 200 diseases[2]. Each year, billions of dollars are invested in clinical research and trials. The failure rate of these trials is an astounding 80%. For the 20% that are successful, the risk of failure before completion of trials for temperature-sensitive drugs and biologicals is ever present due to the possibility of simple cold chain failures. The concern for loss of temperature-sensitive clinical trial materials is high as their loss may result in the delay or negation of clinical data, ultimately delaying product approval by the FDA. This is especially of great concern for emerging biotech companies trying to establish a presence in the marketplace.

Certain temperature sensitive products such as vaccines are at particular risk. The World Health Organization (WHO) estimates that about half of all vaccines are wasted due to temperature excursions as a result of poor cold chain control[3]. Among these vast losses, 80% are due to freezing. Most people think of high temperatures as the danger to temperature-sensitive drugs such as biologics, but it is often low temperatures that cause degradation of these products.

Some vaccines, for instance, are particularly susceptible to freezing temperatures. Freezing can irreversibly reduce the potency of vaccines required to be stored at 2°C to 8°C, resulting in an inadequate immune response in the recipient. Although the potency of the majority of vaccines can be adversely affected by temperatures that are too high, these effects are typically more gradual, predictable, and smaller in magnitude than losses resulting from temperatures that are too cold[4].

Loss of temperature-sensitive drugs such as vaccines can have an enormous global impact. According to WHO, during 2003 more than two million childhood deaths were averted by immunization, as well as an additional 600,000 hepatitis-B-related deaths that would otherwise have occurred in adulthood.

The World Health Organization (WHO) estimates *that about half of all vaccines are wasted due to temperature excursions as a result of poor cold chain control.*

The WHO estimates *that approximately 90% of all cold chain failures are a result of human error.*

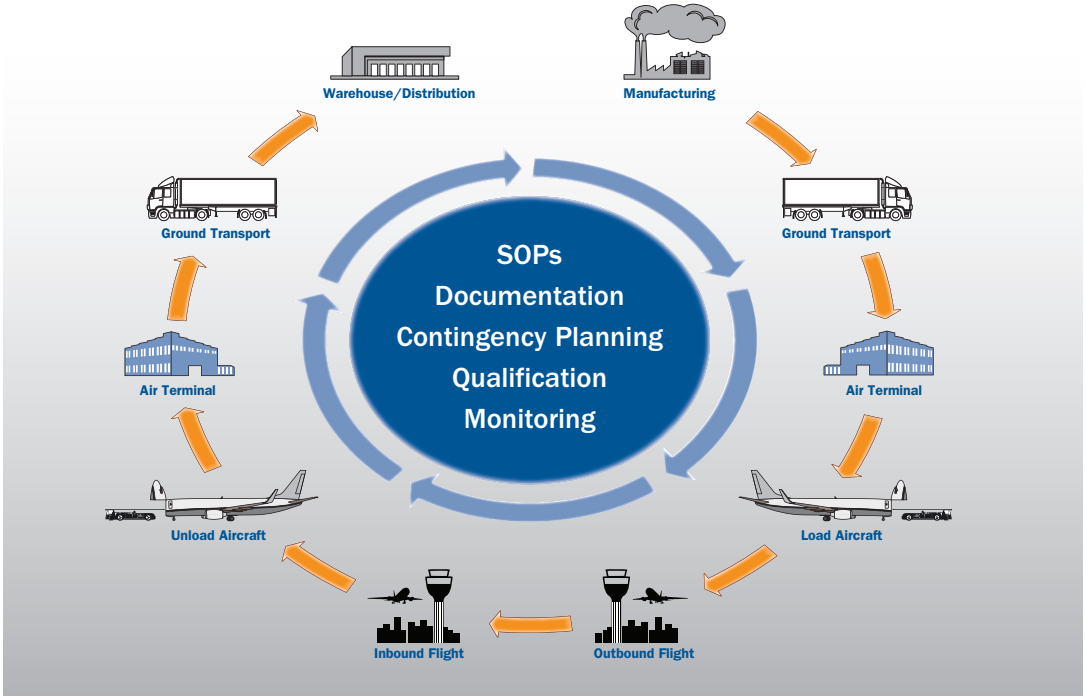
More deaths could have been prevented and illnesses avoided, if vaccines which are sensitive to both excessive heat and cold, were transported and stored correctly[5].

Inadequate procedures or lack of compliance with cold chain regulations and procedures can have catastrophic effects on crucial drug supplies and pose potential risk to the general well-being of the public. For example, in late 1997, a batch of anthrax vaccine that had been spoiled by heat arrived at a U.S. Army facility in Germany. The loss of this scarce resource prompted the Army to order personnel to treat all anthrax vaccine "like a nuclear device"[6]. This illustrates the vulnerability of these types of products and the detrimental results of mishandling. In a recent incident, a major biopharmaceutical manufacturer had to recall three hundred costly packages of vaccine due to temperature excursions during shipment[7]. In a similar case, a major pharmaceutical manufacturer filed a multi-million dollar lawsuit against their contract carrier and its associated airline due to the spoilage of synthetic insulin products that were subjected to open storage and subzero temperatures while awaiting transshipment. The loss of these products is estimated to have cost millions of dollars and could have been prevented.

A Common Thread

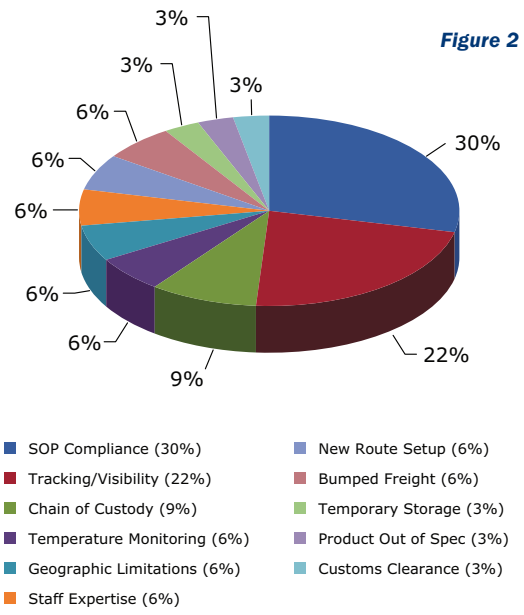
Since a typical cold chain involves the moving of product between multiple storage locations and means of transportation (see *Fig.1*), often involving multiple flights, ground transport vehicles, and staging locations, there are many opportunities for product exposure to temperature extremes. Manufacturers must develop and enforce strict control and compliance measures to ensure that any breach in the cold chain temperature requirements is prevented or, at a minimum, detected and investigated and the product assessed before a temperature-sensitive drug reaches the marketplace.

Basic Cold Chain Transportation Process ***Figure 1***



Areas of Dissatisfaction in Cold Chain Management Processes

Figure 2



Maintaining the cold chain is dependent upon effective training and strict adherence to thorough procedures. The WHO estimates that approximately 90% of all cold chain failures are a result of human error. That's an astonishing figure considering the ever-increasing number of temperature-sensitive biological drug products currently in and entering the marketplace. If such a high number of cold chain failures are attributable to human error, then what is the common thread running through these failures? It may be weak procedures, lack of compliance with procedures, inadequate training, poor supervision, or a lack of knowledgeable management oversight of the cold chain process. A recent survey conducted by Bain and Company of companies engaged in cold chain activities cites SOP compliance as the number one area of dissatisfaction with their current cold chain management processes. (see *Figure 2*)

Life sciences companies can expend substantial time and money in developing cold chain management programs, but because the majority of cold chain failures are a result of human error, there appears to be a large gap in the compliance and enforcement of cold chain procedures and policies. Procedures are only as strong as the information they convey and are only effective when followed properly.

In order to build clear-cut cold chain procedures, one must have a thorough understanding of a drug's stability profile, including how the drug reacts to environmental extremes.

The only way to be certain a temperature-sensitive drug has not been exposed to temperature or humidity extremes is by continuous monitoring throughout the entire cold chain process. This entails both the use of calibrated monitors and an understanding of the effects of time and temperature on the product. Inadequate procedures, which fail to address these issues, can ultimately lead to compromised product, which can have both disastrous financial implications and potentially dangerous health risks.

Every cold chain management program should include procedures and training for contingency plans for worst-case scenarios. For example, if there is a mechanical issue with an aircraft scheduled to transport temperature-sensitive drug product, what should be done with the product until the aircraft is repaired or a replacement aircraft is available? Will the product sit on the tarmac in sub-freezing temperatures or sweltering heat? Will it be held in a warehouse with no environmental controls? These are some of

Every cold chain management program *should include procedures and training for contingency plans for worst-case scenarios.*

*In order **for a cold chain management program to be effective,** there must be a thorough understanding of a drug product's stability profile under stressed conditions.*

the questions that must be addressed when developing contingency plans and supporting procedures for cold chain management.

The importance of adequate procedures and training for cold chain management cannot be stressed enough. Title 21, Code of Federal Regulations 211.142 clearly states that written procedures must be in place for warehousing, including the storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected. In the case of the cold chain, this means that there must be detailed procedures in place that describe the who, what, where, when, and why of the entire process. Since the cold chain often makes use of specialized packaging for shipping materials and storage units, procedures detailing the use of these must be effective and the employees properly trained. No matter how detailed the procedures, a breakdown in the cold chain can result if there is a failure to comply.

Fortifying the Chain

In order for a cold chain management program to be effective, there must be a thorough understanding of a drug product's stability profile under stressed conditions. This knowledge of how a product reacts under specific temperature fluctuations in relation to time of exposure can determine whether a product is still safe and viable or whether it will be wasted after a temperature excursion occurs. This knowledge also determines the parameters against which a thermal shipping container is tested as well as the allowable time out of refrigeration for the product.

As with any process in a regulated industry, the cold chain must be qualified, including the equipment used for transport and storage. This includes determination of the type of packaging that is used, as well as temperature mapping and monitoring of the transportation vehicles, aircraft, and warehouses in order to develop an overall profile of each shipping lane.

There are many cold chain packaging materials and configurations commercially available. Comprehensive shipping studies must be performed in order to determine which packaging materials and configurations work best for a particular product.

Pre-qualified temperature-maintaining packaging is a prominent option in the market. These containers, both passive and active, vary in size and construction materials. Passive containers typically employ the use of frozen gel packs inserted into slots within an insulated container. Active containers usually have a battery operated cooling or convection system. However, it is ultimately the responsibility of the drug manufacturer to ensure that the packaging truly meets the needs of the product being shipped.

Where time is a factor (some containers are qualified to maintain a particular internal temperature for a specified period of time) alternate shipping routes or methods must be qualified as part of the overall cold chain process.

Once packaging for shipment has been determined, shipping studies must be performed to ascertain the various environmental effects on the temperature-sensitive drug during all phases of the cold chain. Properly documented temperature profiling

of refrigerated truck trailers, aircraft cargo holds, and warehouse coolers via the use of electronic monitoring devices is a helpful tool in determining the adequacy of a particular cold chain solution. Additionally, routine in-transit temperature monitoring is essential in assuring the quality of the product. Since different drug products have different stability profiles, one cold chain solution may not work for all products.

Manufacturers must also make sure that their packing and shipping configurations are acceptable under DOT and FAA regulations. For example, there are limitations on the amount of dry ice that can be transported on an aircraft. Depending on the size of a particular shipment, manufacturers may have to find alternative temperature-maintaining shipping containers in order to get their cold chain products to their destination.

Monitoring of product throughout all stages of the cold chain is essential in ensuring the integrity of the product. It is common practice to use electronic monitoring devices to record temperature readings at defined intervals throughout the cold chain and to capture any excursions and their duration. It is recommended that in the case of air transport, various locations within the cargo area of the aircraft should be profiled in order to ensure the protection of product.

Regulations and Guidance

There are several regulations and guidance documents available to aid the industry in developing cold chain programs. Current legislation and guidelines dealing with cold chain management include:

21 CFR 211.142 and 211.150 (storage and distribution) (USA)

USP Chapter 1079: Good Storage and Shipping Practices (USA)

PDA Technical Report No. 39: Cold Chain Guidance for Medicinal Products

MHRA Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03)

WHO – Good Distribution Practices for Pharmaceutical Products

WHO – Good Manufacturing Practices and Inspections, Volume 2, Quality Assurance of Pharmaceuticals

Food and Drug Regulations, section C.02.015 (Canada)

Guidelines for Temperature Control of Drug Products during Storage and Transportation (Guide – 0069) (Canada)

USP Chapter 1079: Good Storage and Shipping Practices is quickly becoming a standard by which many regulatory bodies are auditing. It has been reported that biopharmaceutical companies are being audited by the FDA and other regulatory agencies against the requirements of USP <1079> and the FDA is issuing FDA-483s to major pharmaceutical companies with major supplies.

Since different drug products have different stability profiles, ***one cold chain solution may not work for all products.***

For example, during flight the aft door area of the cargo hold of an aircraft is likely to exhibit lower temperatures than the center of the cargo area. Once the aircraft is on the ground, the opposite may be true during summer months.

The Use of Third Party Carriers

Some manufacturers who lack the in-house resources and expertise for developing and maintaining a thorough cold chain rely on third party logistics (3PL) providers to provide transport, storage, and distribution of temperature-sensitive drugs and biologics. Although some 3PL providers are taking the initiative to address the concerns of manufacturers surrounding the transportation and distribution of these temperature-sensitive products, the ultimate responsibility of ensuring an effective cold chain lies with the drug manufacturer.

As with any supplier, life sciences companies must qualify and monitor their 3PLs. A high level of vendor management, including vendor qualification activities, quality agreements, robust procedures, training, and continuous monitoring, must be in place.

Failure to ensure that the proper controls are in place during transportation by a third party can result in action being taken by the FDA. For example, in late 2006 a major medical device manufacturer was issued a Warning Letter that included a citation for failure to establish and document that the trucking company transporting finished product from the manufacturing plant to the distribution center was protecting materials and finished product from damage and contamination, as specified in a company procedure. Further, it was cited that the trucking company did not have a climate control system in the trailer to monitor temperature conditions[8].

In 2008, the FDA conducted inspections of drug warehouses of varying sizes. Forty two inspections were conducted, and sixteen inspections resulted in the issuance of an FDA 483[9]. The most common observations included:

- Lack of equipment calibration
- Lack of procedures or documentation for investigations into excursions
- Lack of documentation indicating that labeled conditions were maintained during transport

Of all critical / major deficiencies recorded by the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) Good Distribution Practices (GDP) inspectors during 2005 and 2006, 32 percent related to the control and monitoring of storage and transportation temperatures[10]. The MHRA identifies cold chain transportation as one of the top 10 critical / major GDP deficiencies for 2004 through 2006 with temperature control and monitoring during storage being the number one deficiency for all three years[9].

The Parenteral Drug Association's Pharmaceutical Cold Chain Discussion Group (PCCDG) Technical Report 39, *"Cold Chain Guidance for Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment,"* can assist companies in qualifying cold chain packaging configurations. The World Health Organization, in Working Document QAS/04.068, says that special storage conditions for sensitive products should be "provided, checked, monitored, and recorded."

The message in all of these regulations and guidance is clearly the same: the integrity of temperature-sensitive drug products must be maintained throughout the entire cold chain.

Conclusion

With the growing number of temperature-sensitive biologicals on and entering the market, it is imperative that pharmaceutical and biotech companies ensure that the integrity of their products is maintained throughout the entire supply chain by developing robust cold chain processes.

An effective cold chain program can be achieved through properly identifying the critical steps of the entire process and the development of, and compliance with, effective procedures, training, and monitoring. To do this, a thorough knowledge of a product's stability profile to determine proper packaging and containers for shipping is crucial. Just as critical is the qualification of cold chain equipment, warehouses, and shipping lanes to reduce the risk of product exposure to environmental extremes.

In instances where third party vendors are utilized in the cold chain, adequate vendor qualification and management, with an emphasis on cold chain requirements, is essential. This includes making sure that the third party contractor understands the requirements for the handling of specific products and that they have been provided with adequate procedures and training to do so.

Contingency planning is another key step in ensuring there are no breaks in the cold chain process. This includes strategies for dealing with cold storage equipment failure at warehouses and distribution centers, as well as failure of temperature controlled transport equipment. The type of temperature-maintaining shipping container and specific shipping configuration a manufacturer chooses can determine the amount of time that can pass between failure of cooling equipment and transfer to another means of cold storage without damage to the product.

With the growing number of temperature-sensitive drugs on the market, regulatory agencies are actively auditing pharmaceutical and biotech companies for cold chain compliance. This has resulted in the FDA issuing 483s and Warning Letters for deficiencies related to cold chain activities. These actions can be avoided through the development and implementation of thorough cold chain programs.

Manufacturers must be diligent in developing and maintaining cold chain compliance programs to ensure that their temperature-sensitive products remain safe and effective. Ultimately, a successful cold chain compliance program benefits both the manufacturer and the consumer.

It is imperative that pharmaceutical and biotech companies ensure *that the integrity of their products is maintained throughout the entire supply chain by developing robust cold chain processes.*

References

[1] Pharmaceutical Commerce, April 9, 2010

[2] 2008 Guide to Biotechnology, Biotechnology Industry Organization, Guide to Biotechnology (3)

[3] Cold Chain Management Briefing, U.S. Army Medical Material Agency Distribution Operations Center, USAMMA Pharmacy Consultant, Deputy Director for Distributions, MILVAX October, 2006

[4] Notice to Readers: Guidelines for Maintaining and Managing the Vaccine Cold Chain, Centers for Disease Control, Morbidity and Mortality Weekly Report, October 24, 2003

[5] Temperature Sensitivity of Vaccines, World Health Organization, Immunization, Vaccines and Biologicals WHO/IVB/06.10, August, 2006

[6] Vacuum Insulation Maintains Drug Integrity, Pharmaceutical and Packaging News, October, 2000

[7] U.S. Food and Drug Administration Center for Biologics Evaluation and Research, Recalls and Alerts (Freedom of Information Act) May 30, 2006

[8] U.S. Food and Drug Administration Electronic Freedom of Information Reading Room, Warning Letters and Responses, http://www.fda.gov/foi/warning.html

[9] *Can Your Cold Chain Hurt Your Company's Brand?* Dan Schell, Life Science Leader, March, 2010

[10] John Taylor, Quality and Standards Manager, MHRA, August, 2006

Founded in 1962 and serving many of the world's leading life sciences firms, Tunnell Consulting integrates strategic, technical, process, and organizational skills to design and implement sustainable solutions that exactly meet client needs. With deep industry knowledge, extensive scientific credentials, and superior measurable results, we consistently boost the operating performance of each unique client we serve.

Tunnell
STRONGER PERFORMANCE AHEAD

Headquarters
900 East Eighth Avenue, Suite 106 • King of Prussia, PA 19406 • 610.337.0820 • **tunnellconsulting.com**
King of Prussia, PA | Washington, DC