Cold Chain Management - An Essential Component of the Global Pharmaceutical Supply Chain

Rafik H. Bishara, Ph.D.

Executive Summary

Members of the pharmaceutical supply chain have various global regulatory requirements to meet while handling, storing, and distributing environmentally sensitive products. Their focus is to provide cold chain management for temperature sensitive pharmaceuticals to ensure that the quality and efficacy of the product will not be compromised.

This article reviews the increased importance of pharmaceutical cold chain management as a result of changing product portfolios, the requirements for Good Storage and Distribution Practices, current regulatory trends, quality management, risk assessment factors, and temperature monitoring.

Trends include:

- Responsibility for cold chain management ultimately resides with the manufacturer
- Increased oversight, management, and control of environ mental conditions across the entire supply chain (from manufacturer to consumer/patient)
- Increased importance of temperature control and monitoring to mitigate and identify risks
- Heightened priority of patient safety

Due to the presence of multiple uncontrolled variables in the distribution process, developing an appropriate temperature and humidity monitoring program is essential to protect the quality of environmentally sensitive pharmaceutical product and ensure patient safety.

Increased Importance of the Pharmaceutical Cold Chain

Of the greater than $400 billion of pharmaceutical products sold worldwide in 2003 [1] approximately 10% or $41 billion were biopharmaceuticals [2]. From 1999 to 2003 the biopharmaceutical market grew at an average annual compound growth rate of 21% - much faster than the roughly 11% for the traditional pharmaceutical market. Given that biopharmaceuticals tend to be temperature sensitive [3], the cold chain has become an increasingly important component of the overall pharmaceutical supply chain.

The increased investment and management focus on the biopharmaceutical market is due to a number of factors including: a biopharmaceutical's ability to target a significant unmet need, premium pricing relative to other products, and limited generic erosion [2]. While industry forecasts vary, analyst firm ASInsights reports an emerging consensus that the biopharmaceutical market should reach $100 billion by the end of the decade - implying a conservative average annual growth rate of 14%.

Current Regulatory Requirements

Medicines requiring controlled-temperature storage conditions must be distributed in a manner that ensures their quality will not be adversely affected. Following is an overview of key regulatory and industry guidance related to cold chain management. Content covered includes material from World Health Organization, International Conference on Harmonization, Food and Drug Administration, United States Pharmacopeia, Health Canada, and the European Union.

The **World Health Organization's (WHO)** working document QAS/04.068 on Good Distribution Practices (GDP) is applicable to all persons and companies involved in the distribution of pharmaceutical products including the: "manufacturers of intermediate and/or finished products, brokers, suppliers, distributors, wholesalers, traders, transport companies, forwarding agents, processors, etc."[4] This WHO document indicates that the distribution process has generally been "neglected" regarding the: "establishment, development, maintenance and control over the activities involved." Further, because the distribution segment of the pharmaceutical supply chain involves multiple parties, the risks involved become complex. As stated in the (WHO) working document QAS/04.068: "In order to maintain the original quality, every activity in the distribution of pharmaceutical products should be carried out according to the principals of GMP, Good Storage Practice (GSP) and Good Distribution Practice (GDP)."

The (WHO) working document QAS/04.068 states: "where special storage conditions (e.g. temperature and relative humidity) are required during transit, these should be provided, checked, monitored and recorded." It goes on to state: "Temperature mapping of vehicles (where applicable) should support uniformity of the temperature across the vehicle. Recorded temperature monitoring data should be available for review." The overall objective of these guidelines is to: "ensure the quality and integrity of pharmaceutical products during all aspects of the distribution process."

This article is printed in the January/February 2006 issue of American Pharmaceutical Review.
Copyright Rests with the publisher. For more information about APR and to read similar articles,
visit www.americanpharmaceuticalreview.com and subscribe for free.

As stated in the **International Conference on Harmonization document (ICH Q1A (R2))**: "a drug product should be evaluated under storage conditions (with appropriate tolerances) that test the thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use." Furthermore, "data from the accelerated storage condition and, if appropriate, from the intermediate storage condition may be used to evaluate the effect of short-term temperature excursions outside the label storage conditions (such as might occur during shipping) [5]."

The **Food and Drug Administration (FDA)** Guidance on Stability for the industry notes that adverse shipping and/or environmental conditions may affect the product quality [6]. Deficiencies in good distribution practices with specific focus on temperature control and monitoring during shipment have been cited by the FDA [7].

Several studies by the **United States Pharmacopeia (USP)** demonstrated temperature and humidity variations during shipping of drugs and vaccines. Time and temperature recording devices documented values as high as 60°C. [8,9,10,11].

The USP standards are cited in <1079> Good Storage and Shipping Practices. USP <1079> describes procedures to maintain proper storage environments for individual articles and ensure the preparation's integrity until it reaches the user. Risks associated with distribution routes include exposure to temperature excursions, humidity, light and oxygen [12]. Pertinent sections include: "Storage in Warehouses, Pharmacies, Trucks, Shipping Docks, and Other Locations", "Controlled Room Temperature", "Personnel Training", "Qualification of "Cold" Equipment or Stores", "Distribution and Shipment of Pharmacopeial Articles", "Qualification Protocol", "Temperature Challenges", "Receipt of Pharmaceutical Articles", "Distribution or Shipping Vehicles", "Vehicle Qualification", "Pharmaceutical Delivery Staff", "Shipment from Manufacturer to Wholesaler", "Shipment from Manufacturer or Wholesaler to Pharmacy", "Shipment from Pharmacy to Patient or Customer", and "Storage of Physician Samples Handled by Sales Representative in Automobiles".

Recently, **Health Canada** has published guidelines that place greater responsibility on members of the supply chain including manufacturers, distributors, transporters and retailers to ensure that the drug products will reach the customer uncompromised [13].

The key concepts presented in the **European Union Guidance** on Good Distribution Practices include: "The quality system operated by distributors (wholesalers) of medicinal products should ensure that storage conditions are observed at all times, including during transportation" and "products requiring controlled temperature storage should also be transported by appropriately specialized means [14]."

Regulatory Trends

In recent years, global regulatory agencies have increased oversight to ensure the integrity of pharmaceutical products in the distribution chain. Although USP <1079> Good Storage and Shipping Practices, referenced above, had previously been published as an "in-process revision" it was recently published as a "general chapter" in the USP NF 2 Supplement on August 1, 2005. This document in conjunction with regulatory guidances to industry, recent presentations by industry thought-leaders, and regulatory enforcement citations, outlines several common trends impacting cold chain management.

These trends include:

A. Responsibility for cold chain management ultimately resides with the manufacturer

B. Increased oversight, management, and control of environmental conditions across the entire supply chain (from manufacturer to consumer) for temperature sensitive pharmaceutical products

C. Increased importance of temperature control and monitoring to mitigate and identify risks during cold chain transport

D. Heightened priority of Patient safety

A. Responsibility for cold chain management ultimately resides with the manufacturer

Manufacturers are expected to thoroughly understand the stability profile of their products and maintain necessary controls during the distribution process. Examples in Table 1 from the FDA 483 Citation [15] demonstrate the focus on:

- Defining, maintaining and ensuring temperature specifications during shipment (citations A and E).
- Shipping within and maintaining temperature requirements (citations B and H).
- Assurance that temperature and humidity controls are monitored during transportation (citation C).
- Acceptance criteria for storage and movement of material between sites (citation D).
- Transportation study (citation F).
- Standard practice for performance testing of shipping containers (citation F).
- Time out of refrigeration (citation G).
- Validation of shipping carrier (citations I and J).
- Standard operating procedures, records and documentation to ensure the above conditions (citations A, B, D, and F).
- Shipping conditions at various stages of distribution including: general (citations A and B), from manufacturer to third party (citation C), between two sites (citations D and I) or to and from a filing contractor (citation E).

B. Increased oversight, management, and control of environmental conditions across the entire supply chain (from manufacturer to consumer) for temperature sensitive pharmaceutical products

The introduction for USP <1079> states that it is "intended to provide general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures to maintain proper storage environments for individual articles and to ensure a preparation's integrity, including its appearance, until it reaches the user."

Furthermore, USP <1079> references the Prescription Drug Marketing Act of 1987 and the ensuing regulations in 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors stating that these documents represent "necessary regulations and guidance for several legs of the prescription drug distribution chain". The document goes on to state that "manufacturers and distributors should work together to establish proper distribution and product handling requirements for the purpose of ensuring appropriate product maintenance in transit".

C. Increased importance of temperature control and monitoring to mitigate and identify risks during cold chain transport

Thirty-six percent of all critical and major deficiencies recorded by the Medicines and Healthcare Products Regulatory Agency's

This article is printed in the January/February 2006 issue of American Pharmaceutical Review.
Copyright Rests with the publisher. For more information about APR and to read similar articles,
visit www.americanpharmaceuticalreview.com and subscribe for free.

(MHRA) Good Distribution Practice (GDP) inspectors during 2003/2004 related to the control and monitoring of storage and transportation temperatures [16]. Table 2 outlines the United Kingdom Good Distribution Practice Deficiencies recorded in 2003/2004. Compliance issues relating to transportation included: monitoring devices and their location, temperature monitoring records, shipping containers, controlled use of cooling elements, uncertain audit trail, trailer's temperature mapping, contract transport and audit. Other issues included the training of warehouse personnel, drivers, etc., calibration of temperature monitoring devices, returns of cold chain goods, representative's samples, maintenance of the cold chain of imports and maintenance of the cold chain to the patient level.

It is to be noted that a great number of the critical and major deficiencies recorded by the MHRA inspectors in 2003/2004 were related to the control and monitoring of storage and transportation temperatures. As described by the USP in the section on "Distribution and Shipment of Pharmacopeial Articles" in <1079>: once an article leaves the manufacturer's chain of control it enters a complex distribution systems that involves many handoffs, outsourced service providers, and supply chain intermediaries, prior to reaching the patient. It is during this complex stage of distribution when most temperature excursions occur. USP <1079> states: "manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution."

D. Patient safety as a heightened prioritization

Health Canada authorities presented in a recent public forum that they expect the manufacturer to be cognizant of the two regulations of the current GMP's which outline transportation and storage [17]. These are C.02.015 Finished Product Testing - Interpretation 2: "Ensuring that guidelines and procedures are in place and implemented for storage and transportation conditions, such as: temperature, humidity, light control, stock rotation, sanitation and many other precautions necessary to maintain the quality and safe distribution of the drug", and C.02.019 Finished Product Testing - Interpretation 2: Transportation and Storage: "Conditions of transportation and storage which prevent any changes to the potency, purity, and physical characteristics of the drug." Standard operating procedures and records for shipping and receiving are available and contain the following:

- Shipping configuration and the type of protective packaging to be employed for shipping the final product
- Labeling requirements, including storage conditions and special precautions or warnings for shipments
- Mode(s) of transportation approved for shipping
- How shipments of the finished product are to be sealed
- Verifications required to ensure that no finished product in the shipment has been tampered with and that there are no damaged containers
- Evidence that shipping requirements (e.g. temperature control) have been met.

Quality Management System

In order to keep up with the above mentioned global regulatory requirements and trends, a quality management system (QMS) and risk assessment process become essential [18]. Factors to be considered for the QMS may include but are not limited to the: Organization, roles and responsibilities, process, trained resources, implementation plan, compliance, change control, on-time delivery of right product, quality metrics, continuous enhancements, and monitoring customer satisfaction.

Risk Assessment Process

Complementing the QMS for good distribution practices is an ongoing risk assessment process. Areas to be assessed include: compliance with regulations, guidances and quality standards [4-17], product profile, physical and chemical stability[5-7, 19], environment (temperature mapping, temperature control, temperature and humidity monitoring), mode of transportation (ground, air, sea), shipment destination (domestic, export), package (primary and secondary), people (standard operating procedure, training, communication, documentation, recognizing, addressing, correcting adverse events, and change controls).

Temperature Monitoring System

In a recent conference on Cold Chain Management for pharmaceuticals, a speaker from the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) stated: "Each shipment between countries and within countries of large geographical area should be treated as unique in terms of the range of temperatures the goods may experience [16]." Similar temperature monitoring expectations were stated by a speaker from Health Canada [17], and are in the WHO's Good Distribution Practices [4], the USP's Good Storage and Shipping Practices [12], and in the 483 Citations from the FDA Table 1.

The selection of a temperature monitoring system (chemical, mechanical or electronic) is determined by the amount of information required. Given that a majority of manufacturers have classified temperature monitors as a "critical component", most utilize the more sophisticated temperature data loggers from suppliers capable of withstanding quality audits [20]. Electronic temperature data loggers provide valuable information in a convenient format. This includes documentation of temperature and humidity including time and date as well as specific identification. All equipment used for recording, monitoring and maintaining temperature and humidity conditions should initially be validated and

Table 1. Examples of FDA 483 Citations

	Observation
A	August 1998: Standard operating procedures do not describe how kits are packaged or labeled to ensure that temperature specifications are maintained during shipment.
B	January 1999: No records are available to ensure that products are shipped and maintained within their storage temperature requirements.
C	February 1999: There is no assurance that temperature or humidity controls are monitored during the transport of samples from a manufacturer to a third party.
D	May 1999: The standard operating procedure lacks an acceptance criteria for the storage and movement of material between two sites.
E	January 2000: Temperature specifications are not defined for the shipment of a packaged, temperature-monitored bulk products and filled vials to and from the filling contractor.
F	June 2000: No documentation exists for requesting or approving the transportation study of capped tablets for a lot rework. Quality assurance does not approve the "Standard Practice for Performance Testing of Shipping Containers and Systems" procedure.
G	October 2001: Bulk material intended for refrigerated storage is left at ambient conditions for several days before shipping.
H	August 2002: Failure to insure plasma remains at proper temperature
I	March 2003: The shipment by truck of finished vials from one site to another is not yet validated.
J	October 2004, Shipping validation was deficient.

This article is printed in the January/February 2006 issue of American Pharmaceutical Review. Copyright Rests with the publisher. For more information about APR and to read similar articles, visit www.americanpharmaceuticalreview.com and subscribe for free.

thereafter calibrated on a regular basis. Therefore, with regard to in-transit monitoring, manufacturers most commonly incorporate single-use prevalidated electronic temperature data loggers into their cold chain programs [21]. Individual (per-unit) validation certificates offered by leading suppliers, provide a level of quality required for monitoring in the pharmaceutical cold chain. The USP's Monitoring Devices - Time, Temperature, and Humidity <1118> review these standards [12].

Conclusion

Global regulatory requirements for the handling, storage, and distribution of thermally labile pharmaceutical products have emphasized the importance of assuring that product quality and integrity are not compromised in the distribution channel. New guidances outline a comprehensive view of cold chain management across the supply chain including: manufacturers, warehousers, distributors, transporters, and retailers. Trends of recent regulatory inspection citations demonstrate an increased focus on the factors affecting these labile preparations and ensuring their quality and integrity. Due to the presence of multiple uncontrolled variables in the distribution process, developing an appropriate monitoring program is essential.

Table 2. Critical/Major United Kingdom Good Distribution Practice Deficiencies. 2003/2004

Description	%
General storage – temperature control and monitoring	22.8
Lack of or inadequate written procedures	18.3
Premises, equipment, calibration	15.1
Cold storage – temperature control and monitoring	8.9
Quality systems and duties of responsible person	8.9
Housekeeping and pest control	7
Returns	4.4
Cold chain transport	3.8
Stock rotation and control	2.5
Self-inspection	1.3

References

1. "2004 Industry Profile and Healthcare Factbook", Table 281, "Estimated World Pharmaceutical Market by Market Share: 2003" Page 114, Healthcare Distribution Management Association (HDMA).

2. "Biopharmaceuticals, Current Market Dynamics and Future Outlook", pp. 7, 9, 15, and 48, ASInsights Nov. 2003, www.asiinsights.com.

3. "FDA Information Regarding Safety of Food and Biological Products", Distributed via the HAN Info Service, September 2003.

4. Good Distribution Practices (GDP). Working Document QAS/04.68 (RESTRICTED), World Health Organization, Geneva, 2004.

5. International Conference on Harmonization (ICH) Q1A: Stability Testing of New Drug Substances and Products, 2nd Revision, November 2003, originally published in 1994.

6. Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products. United States Food and Drug Administration, 1998.

7. Lucas, T. I., Bishara, R. H., and Seevers, R. H., "A Stability Program for the Distribution of Drug Products," Pharmaceutical Technology, July 2004, pp. 68-73.

8. Okeke, C. C., Bailey, L. C., Medwick, T., and Grady, L. T., "Temperature Fluctuations During Mail Order Shipment of Pharmaceutical Articles Using Mean Kinetic Temperature Approach," Pharmacopeial Forum, 23(3) May-June 1997, pp. 4155-4182.

9. Okeke, C. C., Bailey, L. C., Lindauer, R. F. Medwick, T., and Grady, L. T., "Evaluation of the Physical and Chemical Stability of Some Drugs when Exposed to Temperature Fluctuations During Shipment," Pharmacopeial Forum, 24(5) Sept-Oct 1998, pp. 7064-7073.

10. Okeke, C. C., Bailey, L. C., Medwick, T., and Grady, L. T., "Temperature and Humidity Conditions During Shipment in International Commerce," Pharmacopeial Forum, 25(2) Mar-April 1999, pp. 7949-7959.

11. Okeke, C. C., Watkins, J. W. III, Williams, W., Medwick, T., Bailey, L. C., and Grady, L. T., "A Study of the Temperature and Humidity Variations in the Shipping and Distribution of Anthrax Vaccines," Pharmacopeial Forum 26(3) May-June 2000, pp. 865-882.

12. Genearl Chapter <1079> Good Storage and Shipping Practices, USP 28, Suppl. 2, (August 1, 2005).

13. Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUIDE-0069), Health Canada, October, 2005.

14. Guidelines on Good Distribution Practice of Medicinal Product for Human Use, (94/C63/03), European Union, 1994.

15. Obtained through the Freedom of Information (FOI) Act. www.foiservices.com.

16. Taylor, J., "Cold Chain Management - Ensuring Compliance with Regulations and Guidelines," International Quality and Productivity Center (IQPC) Conference on Cold Chain Management for Pharmaceuticals - Getting the most from your Temperature-Controlled Logistics Strategy, Montreal, PQ, Canada, March 1-2, 2005.

17. Antonetti, T. "Complying with New and Proposed Regulations for Cold Chain Management," International Quality and Productivity Center (IQPC) Conference on Cold Chain Management for Pharmaceuticals - Getting the most from your Temperature-Controlled Logistics Strategy, Montreal, PQ, Canada, March 1-2, 2005.

18. Bishara, R. H., "Product Integrity and Cold Chain Management for Medicinal Products," International Quality and Productivity Center (IQPC) Conference on Cold Chain Management for Pharmaceuticals - Getting the most from your Temperature-Controlled Logistics Strategy, Montreal, PQ, Canada, March 1-2, 2005.

19. Seevers, R. H., Bishara, R. H., Harber, P. J., Lucas, T. I., "Designing Stability Studies for Time / Temperature Exposure," American Pharmaceutical Outsourcing, Volume 6 (5), Sept/Oct, 2005, pages 18, 20, 21, 23, 55.

20. Ames H., Director Life Science Marketing, Sensitech, Inc. Internal Document, (Critical Component Reference).

21. Ames H., Director Life Science Marketing, Sensitech, Inc. Internal Document, (Single-Use vs. Multiple-Use).

Rafik H. Bishara, Ph.D., is the current chair of the Pharmaceutical Cold Chain Discussion Group (PCCDG), Parenteral Drug Association (PDA). Dr. Bishara retired from his position as Director, Quality Knowledge Management and Technical Support, Eli Lilly and Company in December 2004 after a 35-year career with that pharmaceutical company. He received a Ph.D. from Purdue University, Indiana, USA.

To correspond with the author, please e-mail: rafikbishara2@yahoo.com

This article is printed in the January/February 2006 issue of American Pharmaceutical Review. Copyright Rests with the publisher. For more information about APR and to read similar articles, visit www.americanpharmaceuticalreview.com and subscribe for free.