

Good Cold Chain Management Practices for Clinical Trial Materials/ Investigational Medicinal Products

Rafik H. Bishara, Ph.D.

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Introduction

The storage, handling, and distribution of temperature-sensitive drugs represent an increasingly important component of the global pharmaceutical supply chain. Clinical trial material (CTM) or investigational medicinal products (IMP) are an important part of the earliest stages of the life science supply chain. Given the increased number of global regulatory and standards-based guidance documents issued over the past two years, members of the pharmaceutical supply chain are taking notice and making changes to ensure product quality and protect patient safety. The purpose of this paper is to review the various factors affecting Good Cold Chain Management Practices for Clinical Trial Materials/Investigational Medicinal Products.

Importance of Cold Chain

Of the greater than \$565.9 billion of pharmaceutical product sold world wide in 2005, greater than 10% or \$60 billion were biopharmaceuticals [1] [2]. Between 2004 and 2005 the biopharmaceutical market grew 17.1%, much faster than the traditional pharmaceutical market – which grew about 7% over the same time frame [3]. The R&D pipeline remains strong, particularly for products in Phase I and Phase II clinical development. “At the end of 2006 some 2,075 molecules were in development, up 7% from 2005 levels, and up 35% from the end of 2003. In addition, a promising range of drugs are now in Phase II clinical trials or pre-approval stage. Of the total pipeline, 27% of these products are biologic in nature” [4].

Cold Chain Challenges

Clinical trials are being run on a global scale and in some cases in markets with less than ideal logistics infrastructure. The complex clinical supply chain creates a challenging distribution environment because of shipping large volumes of refrigerated patient kits worldwide while maintaining and

documenting appropriate environmental conditions. Given the great number of clinical sites, there is increased complexity for maintaining product quality and mitigating the risk of thermal excursions.

John Taylor, Quality and Standards Manager for UK Medicines and Healthcare Products Regulatory Agency stated: “Emerging markets for clinical trials in Asia, South America, Eastern Europe, and expanding markets in traditional clinical trials territories, present challenges to shipping companies regarding the quality maintenance of products in transit” [5]. The globalization of clinical trials is driving programs in more remote locations. This has fueled the need for personnel to work with specialty couriers, contracted depots, and shipper manufacturers to improve the performance of the supply chain and build a more robust clinical trial distribution process. Specialty service providers have responded to changing market needs. For example, an organization has developed Cold Chain Specialist positions within its Clinical Services. “These personnel work with courier, depots and shipper manufacturers to improve the performance of the supply chain and build a framework of procedures and best practices to drive down the out of specification results” [6].

Further support of these points has been discussed: “One of the most significant factors affecting the potency of medicinal agents is the ability to maintain them in controlled environments.” “Maintaining the chemical and therapeutic integrity of investigational medicinal products poses special cold chain challenges, since clinical trials require multiple small shipments to as many as 300 study sites worldwide” [7].

Impact of Cold Chain Failure on Clinical Trial Material

Temperature excursions during the storage, handling, or distribution of temperature-sensitive clinical trial material pose significant safety and financial risks.

Cold chain failure may lead to 4 key risks:

1. The patient could be administered an unsafe product
2. A lack of compliance with global regulatory and standards-based requirements can increase liability
3. Thermal variability can lead to inconsistency of results between and within batches
4. The shipment can be rejected by the Quality department therefore leading to costly delays – increasing the complexity of trial management [8]

Service Providers and Partners

Many clinical trials include the shipping, distribution, and delivery of temperature-sensitive articles whether it is the study drug, the clinical specimens, or the ancillary supplies. As such, cold chain pre-qualified packaging plays a critical role in safely and effectively transporting the temperature-sensitive items shipped in small amounts in high frequency to the clinics. “Vendors have to prove their packaging and insulated container/refrigerant systems provide adequate protection for temperature-sensitive items. As supply chains grow more complex, product life cycles decrease and regulatory authorities become increasingly concerned about product integrity during delivery” [9].

In a case history review, the author indicated that partnering with a provider of transportation packaging for temperature-sensitive products (TSPs), was a critical step in developing solutions for individual and bulk shipments of clinical trial materials. This is important as unlike commercial shipments of TSPs, the shipment value for clinical trial materials is not a reflection of the value of the product, but it is the ability to deliver the study drug being tested in a way that assures the

timely completion of the clinical trial [10].

Many pharmaceutical manufacturers have set a goal to streamline clinical trial logistics. In cooperation with worldwide transportation and logistics providers, a closed-loop clinical supply chain may be established. Services include shipping, warehousing, customs brokerage, logistics management, and a centralized record keeping - ensuring the integrity and traceability of the materials in a predictable manner. Temperature-controlled transportation and documentation including monitoring capabilities should be included [11].

Recently, the pharmaceutical industry has progressed from the point of shipping being an afterthought to exact controls on materials/product in-transit and proof of custody at the destination. The pharmaceutical developer/manufacturer is paying attention to temperature and/or physical conditions which may affect the good storage and good distribution practices (GSP/GDP) of their materials/products. Documentation and control of the storage, handling, and distribution for temperature-sensitive goods is most appropriately addressed through a sound shipping qualification. “The cold/frozen chain Shipping Qualification is a process involving integration of the shipping system, the product and the transportation medium/route. The partners in this process: the packaging designer/manufacturers, testing labs, product development scientist, corporate owners of the product, carriers and shipper vendors, mutually work together to produce the best system for the entire cycle of shipping and storage.” Further supporting the need for a detailed shipping qualification is fueled by the debate between appropriate shipping and storage temperatures. “For example, some products may be at -20°C +/-5°C for storage, but in shipping, -15° to -60°C is more realistic. This difference requires supporting data and a transportation control strategy. Temperature monitoring and excursion investigation procedures are the most appropriate methods for documenting quality and the affect of the distribution environment. As a result, Quality Agreements between pharmaceutical manufacturers and their supply chain partners are used to manage the complex process [12].

Regulatory Trends

Four primary regulatory trends have been identified:

1. Accountability for the cold chain ultimately resides with the Manufacturer but responsibility is shared across all supply chain partners
2. Increased oversight, management, and control of environmental conditions across the entire supply chain
3. Increased importance of temperature control and monitoring
4. Heightened priority of patient safety – with focus on product quality [13]

Geoffrey Glauser, Former Director of Logistics at Fisher Clinical Services stated: “FDA is focusing more on the supply chain control of pharmaceuticals or biologicals.” “The establishment of that control needs to start with clinical materials, the associated known stability data for the drug, and how the manufacturer has maintained the environment throughout the entire supply chain” [14].

Global Regulatory and Standards-Based Requirements

Remaining compliant with global regulatory requirements for the storage, handling, and distribution of clinical trial materials can be a daunting task. While the requirements tend to be similar for both investigational drugs and finished goods, it is imperative to first understand the specific requirements for the countries in which a trial will occur. For example, John Taylor and Ian Holloway from the Medicines and

Healthcare Products Regulatory Agency in United Kingdom state in a recent article: “Organizations shipping clinical trial materials in Europe and within Europe should be aware of the need to comply with relevant standards of good storage and shipping practice. Those standards are the same irrespective of whether the product is for investigational purposes or is a licensed one. In some cases, the need for control is even greater for clinical trial materials because, in early phase studies, the stability of the material may not have been fully established. The redeployment of clinical trial materials to different trial sites can present additional risks to these materials” [15].

The regulations outline that cGMPs apply to the manufacture of clinical trial materials. The preamble No. 49 of the FDA’S 21 CFR part 210 and 211 cGMPs states, “...these cGMP regulations apply to the preparation of any drug product for administration to humans or animals, including those still in investigational stages” [16]. ICH Q7A Section 19 (Requirements for the Manufacture of API for clinical supplies) indicates that, “a system should be in place to ensure that information gained during development and the manufacture of APIs for use in clinical trials is documented and available” [17].

The International Conference on Harmonization (ICH) Topic E6 “Good Clinical Practice: Consolidated Guidance” 1997 is a commonly referenced industry document. This guidance was developed by an ICH Expert Working Group and received input from regulatory authorities. ICH E6 has been adopted by the regulatory bodies of the European Union, Japan, and the USA.

Section 5.13 “Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)” – 5.13.2 of ICH E6 states: “The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions, (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, store managers) of these determinations.” Furthermore, Section 5.13.3 states: “The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.”

Section 5.12 “Supplying and Handling Investigational Product(s)” – 5.14.3 states: “The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s)... 5.14.5 states: “The sponsor should take steps to ensure that the investigational product(s) are stable of over the period of use.”

The European Commission Volume 4, Good Manufacturing Practices, Annex 13 Manufacture of Investigational Medicinal Products provides quality standards for IMPs. The overarching principal of this document states: “Investigational medicinal products should be produced in accordance with the principles and detailed guidelines of Good Manufacturing Practices for Medicinal Products (The rules governing Medicinal Products in the European Community, Volume IV).” Annex 13 goes on to state: “The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture.” Sections of Annex 13 that are particularly relevant to the storage, handling, and distribution of temperature-sensitive goods include “Documentation – Product Specification File, Manufacturing Formulae and Processing Instructions”, “Production – Packaging, Labeling”, “Quality Control”, “Release of Batches”, “Shipping, and Recalls and Returns.”

Clinical trials demand fast and stress-free delivery. As a result, air transport has been involved in many aspects of the drug delivery process and the world of pharmacopeia in general. Clinical research organizations and university institutions that use laboratory or specific pathogen free animals in the research all rely on air transport to a large extent. The Perishable Cargo Manual (PCM) of the International Air Transport Association (IATA) provides good cold chain management practices specific to air transport. The recently published 8th edition of the PCM includes a new chapter, 17 titled: “Air Transport Logistics for Temperature-Sensitive Healthcare Products” [18,19].

While the above documents provide helpful guidance, all applicable local requirements and regulations need to be reviewed and considered. For example, Health Canada Guide-0069 “Guidelines for Temperature Control of Drug Products during Storage and Transportation” states: “These guidelines not only apply to drugs for human and veterinary use but also to clinical trial drugs for human use” [20]. Furthermore, Parenteral Drug Association’s (PDA) Technical Report No. 39 - Revised 2007: “Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment” states: “The process defined in this document is for temperature controlled transportation of medicinal products. The same principles may also be applicable for investigational products, intermediates, excipients, active pharmaceutical ingredients (APIs), and diagnostic products that require temperature controlled transportation” [21].

The previous examples are just a few of the existing regulatory and guidance-based standards, they provide a solid background on Good Cold Chain Management Practices related to the storage, handling, and distribution of clinical trial materials.

The following insert is a compilation of pertinent references covering good cold chain management practices for clinical trial material.

21 CFR, Volume 5, Part 312, Investigational and New Drug Application	Volume 4, Good Manufacturing Practices, Annex 13, Manufacture of Investigational Medicinal Products – July 2003
PAHO – Good Clinical Practices Document of the Americas	Health Canada - Guidance for Clinical Trial Sponsors, Clinical Trial Applications – June 11, 2003
2006 No.1928, The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006	Directive 2001/83/EC – November 2001
MHRA Guidance Note No. 6, Notes for Applicants and Holders of Wholesale Dealer’s License – Revised August 2006	Directive 2001/20/EC – April 2001
Commission Directive 2005/28/EC – April 2005	EMA, VICH Topic GL9 (GCP) Guideline of Good Clinical Practices – July 4, 2000
Statutory Instrument 2004 No. 1031, The Medicines for Human Use (Clinical Trials) Regulations 2004	WHO – Standard Operating Procedures for Clinical Investigators – March 1999
Commission Directive 2003/94/EC – October 2003	Health Canada – Guidance for Industry, General Considerations for Clinical Trials, ICH Topic E8 – 1997
ICH E6 Good Clinical Practice Consolidated Guidance – April 1996	

Conclusion and Recommendations

The growth in the bio-pharmaceutical market combined with the complexity of the clinical supply chain and global regulatory environment require that all supply chain partners are aware of appropriate regulations, local requirements, Pharmacopeial standards, and industry best practices related to the storage, handling and distribution of temperature-sensitive products. Regulatory guidance and inspectional trends demonstrate a focus on Good Cold Chain Management Practices. All partners should have the distinct common goal ensuring that each

patient and site is supplied with the correct medication at the right time and in the right condition.

NOTE: The concept of Good Cold Chain Management Practices for Clinical Trials Materials/Investigational Medicinal Products was presented at the PDA Annual Meeting, Pacific Region Clinical Supplies (PARCS) Conference, and Sensitech and World Courier sponsored Webinar [8,22,23].

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Rafik H. Bishara, Ph.D., is the current Chair of the Pharmaceutical Cold Chain Interest Group (PCCIG), Parenteral Drug Association (PDA). Dr. Bishara has served as a Temporary Adviser to the World Health Organization (WHO) since July, 2007.

Dr. Bishara retired from his position as Director, Quality Knowledge Management and Technical Support, Eli Lilly and Company after a 35-year career. During his tenure at Eli Lilly and Company, Dr. Bishara was responsible for the Quality Knowledge Management, Global Compendial Affairs, Stability and Distribution Excellence, Global Product Protection, Special Security Substances and Controlled Substances Administration. Dr. Bishara frequently chairs and presents at industry leading conferences, has authored numerous articles, and technically advised several organizations on Good Cold Chain and Temperature - Controlled Management Practices. Dr. Bishara received his Ph.D. from Purdue University, Indiana, USA.

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

