

FDA & ICH: Regulations and Standards for Temperature-Controlled Supply Chains



The two greatest risks in pharmaceutical and biotechnology supply chains are the risk of product becoming adulterated during transport and the risk of non-compliance with federal regulations, guidelines and standards. After that the greatest concern of manufacturers and distributors is cost containment in an increasingly globalized, increasingly complex supply chain.

Two organizations that carry significant regulatory weight are the combined forces of the US Food and Drug Administration (FDA) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The FDA co-founded the ICH with the European Community in 1990 with the goal of creating a globally harmonized approach to the understanding and application of technical guidelines for drug manufacturers. The outcome of harmonisation was to decrease unnecessary replication of costly regulatory processes, thereby promoting more efficient manufacturing, processing and distribution methods for regulated products on a global scale.

Whereas the jurisdiction of the FDA is primarily in the United States and Puerto Rico, the ICH is an international entity that involves the US, Japan and the European Union. Other parties involved in ICH include:

- The Pharmaceutical Research and Manufacturers of America (PhRMA)
- The Center for Drug Evaluation and Research (CDER)
- The Center for Biologics Evaluation and Research (CBER)
- The European Commission
- The European Federation of Pharmaceutical Industries Association
- The Japanese Ministry of Health, Labor and Welfare
- The Japanese Pharmaceutical Manufacturers Association
- ICH Secretariat¹
- The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)
- And other ICH sponsors: Health Canada, the European Free Trade Area (EFTA), and the World Health Organization²

In this application note we look at the FDA regulations and ICH guidelines that address supply chain management for temperature-controlled pharmaceutical and biotechnological products, including:

- ICH Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products
- ICH Harmonised Tripartite Guidelines Q6A and Q6B (Test Procedures and Acceptance Criteria for New Drugs and New Biotechnology)
- FDA CFR Title 21 203.32, 203.36, 211.150
- FDA 483 observations on cold chain applications with suggested deviation offsets

Moving temperature-sensitive products necessarily renders the supply chain a “cold chain” (sometimes also called “cool chain”) and products that fall under the purview of federal law and enforcement agencies further evolves the logistics process into a *regulated* cold chain.

However, there is currently no single standard, guidance, regulator, document or arbiter with the final say on a compliant cold chain for a given region.³ Instead, manufacturers and distributors face a myriad of regulations, conferences, technical reports and recommendations from disparate agents.

A growing list of documents, legislation, requirements, recommendations and guidelines reveal how fragmented the current regulatory environment is in cold chain management:

- The EU Guide to Good Manufacturing Practice, Annex 13
- The Guidelines on Good Distribution Practice (GDP) of Medicinal Products
- CDC Guidelines for Maintaining and Managing the Vaccine Cold Chain
- WHO Guidelines on the international packaging and shipping of vaccines
- PDA Technical Report 39
- The US Code of Federal Regulations
- US and European Pharmacopoeia

A Scientific Approach to Cold Chain Management

To simplify your approach to cold chain management into a principle, ask yourself what any regulatory body (and inspector) will want to know. From a regulatory standpoint, the question always comes down to the quality and completeness of your scientific (that is, verifiable) knowledge of a product and the environments it moves through before reaching the end user. A common introduction to many an FDA Form 483 observation is:

“Your firm did not establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, product containers, in-process materials, and transport methods conform to appropriate standards of identity, strength, quality and purity.”

As in all FDA-regulated applications, establishing and documenting data on your operating environments that are “scientifically sound” should be your underlying goal in compliance efforts. Cold Chain Quality engineers, Cold Chain managers, Packaging engineers and other stakeholders must understand their environmental conditions and product parameters better than any inspector. After the knowledge of conditions and parameters is established comes the documentation of that knowledge, without which, it may as well not exist.

In the following sections, we review some of the main FDA and ICH regulations and guidelines concerning supply chain applications. We'll also provide some samples of 483 observations and discuss what sort of corrective and/or preventive actions could offset the (possible) deviations in the samples.

ICH Guidance

The ICH publication: “Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products”⁴ describes proper management of temperature excursions in shipping and short-term storage applications. For testing and acceptance criteria of closure systems for new drugs

(chemical) and new biotechnology, refer to these guidances:

- Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products⁵
- Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- Q6B Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

While not specific to distribution applications, these guidances contain valuable criteria for creating tests that will ensure products are protected during shipping and short-term storage. A crucial element to creating a compliant cold chain is to create tests that accurately represent the real-time, real-world shipping environment, including primary and secondary containers, transport and storage durations, seasons and climatic zones.

It should be remembered that the ICH guidelines aren't standards; rather, they are “guidance for meeting technical requirements...” and “...are intended to be used in combination with any regional requirements...”⁸. Quality managers, cold chain engineers, and anyone whose responsibilities include a temperature-controlled supply chain are accountable for understanding ICH recommendations. FDA inspectors often cite non-adherence to ICH, as seen here in this Warning Letter:⁹

“Please note that a guidance document entitled “Q7A Good Manufacturing Practice Guidance of Active Pharmaceutical Ingredients” (ICH CGMP Guidance), prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), describes current good manufacturing practice (cGMP) ...

Although the ICH cGMP Guidance does not impose requirements, [the] FDA considers its recommendations,

as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's [products] have been manufactured, processed, packed, and held according to current good manufacturing practice under Section 501(a)(2)(B) of the Act.”

In the Q5 guideline, under “Storage Conditions Part 6.3, Accelerated and Stress Conditions”¹⁰ the ICH recommends that stress tests be performed in order to define the conditions that may occur during transportation will affect the product. To recommend testing, the guide is necessarily broad because of all the different types of products that might be shipped. The testing will not only determine the conditions that impact the product, but should also determine which tests are best for determining stability.

“Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. ...Conditions should be carefully selected on a case-by-case basis.”¹¹

Likewise for new drug substances and products:

“Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).”¹²

Food & Drug Administration (US)

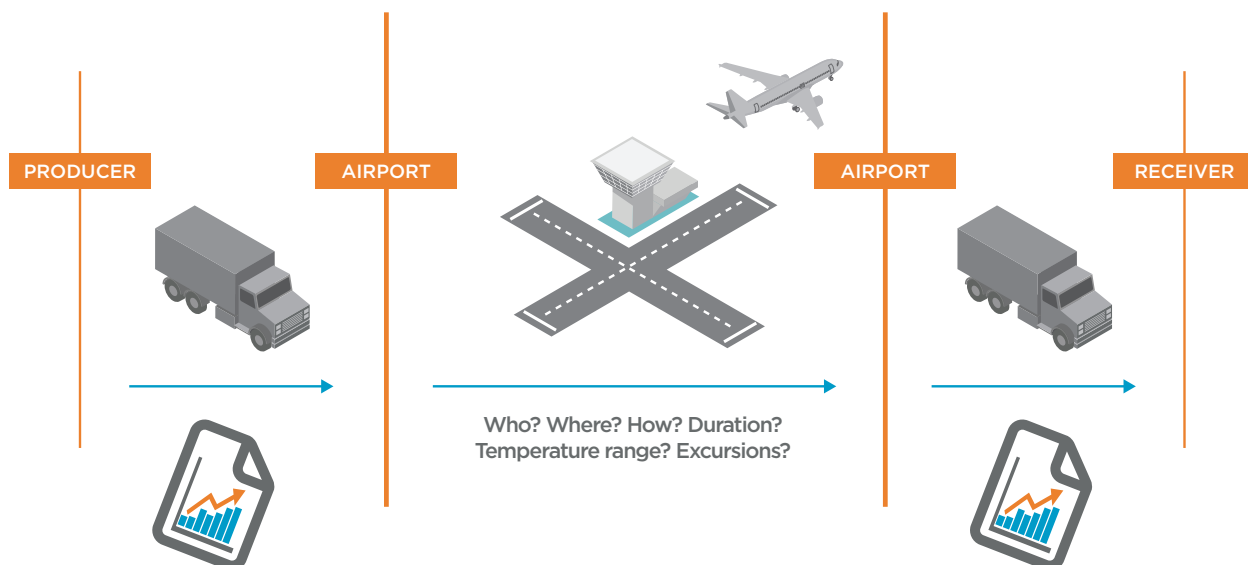
Three key regulations from the FDA that address cold chain are:

- 21 CFR 203.32 “Prescription Drug Marketing – Drug sample storage and handling requirements.”
 - This subpart (D–Samples) contains two parts that stipulate that (a) “Storage and handling conditions” not adversely affect the drug and (b) manufacturers, distributors of record, and their representatives comply with all compendial and labeling requirements.¹³
- 21 CFR 203.36 “Fulfillment houses, shipping and mailing services, comarketing agreements, and third-party recordkeeping” looks at “comarketing agreements” with any third party involved in shipping and storing drug samples. This section states that the manufacturer or distributor is responsible for record keeping and documentation and must comply with the Prescription Drug Marketing Act (PDMA) and amendments. The PDMA document contains recommendations relating to 21 CFR Parts 203 and 205 and outlines how to document drug products that pass from manufacturers to Authorized Distributor of Record (ADR) and provisions regarding pedigrees.¹⁴
- 21 CFR 211.150 of Subpart H: Holding and Distribution - “Distribution procedures” states that these products must be shipped within: “...appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the United States Pharmacopeia/National Formulary (USP/NF).”
 - “(2) Appropriate manual, electromechanical, or electronic temperature and humidity recording equipment, devices, and/or logs shall be utilized to document proper storage of prescription drugs.”
 - “(3) The recordkeeping requirements in paragraph (f) of this section shall be followed for all stored drugs.”
 - “(f) Recordkeeping” states that drug distributors must maintain records and inventories that show receipt and distribution or “other disposition” of prescription drugs. These records must include the source of the drugs, the address of the location that the drugs were shipped from, the identity and quantity, and the dates of receipt/distribution/other disposition. Records must be kept and accessible for inspection for 3 years after the date of their creation.¹⁵

The regulations reveal what one expects: documentation is key to compliance with federal regulations. Unfortunately, the supply chain has many links; each requires thorough records and many stakeholders can contribute to a document portfolio of a given product in the chain.

Stakeholders typically include drug or biotechnical testing laboratories and manufacturers, contract manufacturers and packagers, distribution centers, wholesalers, and finally, healthcare facilities or pharmacies. The distribution path can include different types of transportation and several climatic zones, and each new mode of transport and location will come with its own temperature fluctuations.

When setting up a cold chain management system that complies with federal regulations, you’ll need to create or obtain detailed records of stability data, geographical data (including climatic zones), shipping and storage durations at each point in the journey, and contingency procedures for delays, out-of-specification conditions or other unexpected events. In the next section, we’ll look at some common GDP deviations that can occur along the cold chain.



Typical Cold Chain Distribution

Cold Chain 483s

Here are several excerpts from Form 483s¹⁶ that were issued on observations directly related to cold chain management. In the right side of the table we've suggested solutions for avoiding deviations like those excerpted below and maintaining a GDP-compliant cold chain.

Form 483 Excerpt	Suggested Solution
<p>"Standard operating procedures do not describe how kits are packaged or labeled to ensure that temperature specifications are maintained during shipment."</p>	<p>The problem here could be that the SOP lacked the appropriate information even though a package and labeling performance qualification study was done, or the study wasn't done at all. Proper shipping validation would produce a document outlining standard packaging and labeling configuration. SOPs ensure that kits are packaged in the validated configuration and labeled with the applicable temperature specification. Primary packaging should be qualified in the Identification of Requirements process (See: TR39¹⁷ process flow) and included in a Functional Requirements document. Include the packaging summary created for the Functional Requirements in the shipping SOP.</p>
<p>"No records are available to ensure that products are shipped and maintained within their storage temperature requirements."</p>	<p>No record available could mean:</p> <ol style="list-style-type: none"> 1. They monitored but no records were kept, or the records were lost. If the latter, this is a record storage and retention issue. Or, 2. They don't monitor and had no records. <p>What's required is a monitoring program of some sort; however, it must be proceduralized to make sure records are reviewed and maintained.</p>
<p>"The standard operating procedure lacks acceptance criteria for the storage and movement of material between two sites."</p>	<p>This may just be a poor SOP. They might not have had the specifications, but that would have shown up in the Form 483. More likely is that the SOP was just poorly written and/or not well reviewed. Three elements of acceptance criteria are:</p> <ol style="list-style-type: none"> 1. They define the ways that SOP users confirm that the transport and holding processes are functioning as intended. 2. They identify the objective results of a process; they must take into account the product specifications, and process flow requirements. 3. Acceptance criteria must be measurable and verifiable.¹⁸
<p>"Temperature specifications are not defined for the shipment of packaged, temperature-monitored bulk products and filled vials to and from the filling contractor."</p>	<p>They need to get the specifications defined and included in a shipping SOP. A copy of the batch record, stability statement, and/or a Certificate of Analysis (COA) should provide a history of the conditions pertinent to the quality of the final product.¹⁹</p> <p>Contracts should also contain handling instructions for all bulk and finished products.²⁰</p>
<p>"Bulk material intended for refrigerated storage is left at ambient conditions for several days before shipping."</p>	<p>What's required is either an SOP, or a way to make sure the existing SOP is followed. A simple solution may be installing a validated storage environment because one is lacking in the loading/shipping area.</p>
<p>"The shipment by truck of finished vials from one site to another is not yet validated."</p>	<p>A gap in qualifying the entire flow of transportation indicates a lack of identifying the transportation process and performing the necessary qualifications outlined in PDA TR39.¹⁷</p>

Conclusion

The goal of any supply chain is to transport products from the manufacturer to the consumer. However, the success of a supply chain depends on and is measured by its ability to deliver products that can serve their ultimate purpose with the end user. In pharmaceutical supply chains, this means that a product must arrive unadulterated and with its efficacy fully intact. In the context of a successful supply chain, organizations that enforce regulations and create quality standards act not only as arbiters, but as partners in quality. With globalization and emerging markets, many countries look to ICH and the FDA for guidance in approaches to improving supply chain control and performance. It follows that basing your regulatory compliance firmly in the regulations, standards and guidelines of these two organizations will ensure that the fundamental requirements of a safe supply chain for drugs and biotechnology are satisfied.

Sources

¹ Oversees documentation

² From: "ICH and FDA: A Valuable Cooperative" by Corrine Knight and Annette Dunn, <http://www.CodaCorpUSA.com/blog> or <http://blog.CodaCorpUSA.com/2010>

³ "Preserving the Cool Chain," Mary Simpson, Edith Penxten, Elie Dechesne, http://www.pharmaceuticaloutsourcing.com/pdf/POD001_054E_Bristol-Myers.pdf, retrieved 5/22/2012

⁴ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf>, retrieved 6/25/2012

⁵ ICH Harmonised Tripartite Guideline: Quality of Biotechnical Products: Stability Testing of Biotechnical/Biological Products Q5C http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/O5C/Step4/O5C_Guideline.pdf, retrieved 5/23/2012

⁶ The full name of ICH is the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use" Source: <http://www.ich.org/about/faqs.html>, retrieved May 22, 2012

⁷ Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm128204.pdf>

⁸ See ICH Work Products, "Are the ICH Guidelines 'standards'?" <http://www.ich.org/about/faqs.html>, retrieved 5/22/2012

⁹ <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/ucm076496.htm>

¹⁰ Q5 – Stability Testing of Biotechnical/Biological products

¹¹ Page 8, Q5– Stability Testing of Biotechnical/Biological products

¹² Page 9 Stability Testing of New Drug Substances and Products http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2_Guideline.pdf

¹³ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=203>, retrieved 5/22/2012

¹⁴ A drug pedigree is a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them. See CPG Sec. 160.900 Prescription Drug Marketing Act – Pedigree Requirements under 21 CFR Part 203 <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073857.htm>, retrieved 6/14/2012

¹⁵ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=205.50>, retrieved 5/22/2012

¹⁶ <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/default.htm>, obtained through the Freedom of Information (FOI) Act at the FDA electronic reading room, accessed 5/22/2012

¹⁷ Parenteral Drug Association's "Technical Report No. 39 Revised 2007 Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment" covers the methods of qualifying the cold chain applications.

¹⁸ "IPEC-Americas Certificate of Analysis Guide for Bulk Pharmaceutical Excipients" (Glossary, Page 17) offers a definition of 'acceptance criteria' that can be extrapolated to aid in understanding acceptance criteria use in SOPs for pharmaceutical manufacturing processes; "The specifications and acceptance/rejection limits, such as acceptable quality level and unacceptable quality level, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch of raw materials, intermediate, packaging material or excipient." It is important to note that acceptance criteria as defined by the IPEC carries an inherent definition of rejection criteria – that is, all that is outside of a minimum or maximum limitation.

¹⁹ "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials" WHO, Page 17 <http://apps.who.int/medicinedocs/documents/s14136e/s14136e.pdf>, retrieved 5/28/2012

²⁰ See also: "Quality assurance of pharmaceuticals" WHO, Page 27: Section 7. Contract production and analysis



For more information on cold chain applications, contact your local Vaisala representative at sales@vaisala.com.

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