

# A Stability Program for the Distribution of Drug Products

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Drug products must be transported in a manner that ensures **products will be maintained within an acceptable temperature range**. The authors outline stability studies designed to evaluate the impact of temperature excursions on product quality that may occur during distribution.

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**S**tability is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating periods (1). Physical, chemical, and microbiological data are generated as a function of time and storage conditions (e.g., temperature and relative humidity [RH]). Stability testing provides evidence that the quality of a drug substance or drug product under the influence of various environmental factors changes with time (2). Although the storage conditions are relatively constant, the distribution environment can vary greatly, especially when a drug product is shipped between various climatic zones (1). Seasonal changes, mode of transportation, and the number of drop-off points are also variables that should be considered within the pharmaceutical supply chain. Drug products requiring controlled-temperature storage conditions must be distributed in a manner that ensures that the product quality will not be adversely affected. With the exception of short transit times within the same climatic zone, it is virtually impossible to validate a shipping method against all environmental conditions.

Therefore, this article outlines distribution stability studies designed to generate additional data to complement pre-formulation development and routine International Conference on Harmonization (ICH) Q1A registration studies. If results from routine studies indicate that the product stability profile is very stable, then one may decide that distribution studies are not warranted. If additional distribution stability studies are needed, they can be developed to test the product's temperature limitations. In the event that a temperature excursion is higher or lower than the recommended storage condition, these data would be examined to evaluate the effect on product quality.

Mean kinetic temperature (MKT) relates to temperature excursions. MKT, as defined by the United States Pharmacopeia (USP), is a "single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures" (3). In nontechnical terms, the MKT converts a variable temperature into an equivalent steady temperature. Then, the steady temperature is used to determine the effect of the excursion on product quality.

**Table I: Distribution of Medicines and Healthcare Products Regulatory Agency citations for 2002.**

Area	Number
General storage: temperature control and monitoring	33
Cold chain: temperature control and monitoring	26
Lack of or inadequate written procedures	21
Returns: handling and records	15
Stock rotation and control	13
Quality system and duties of a responsible person	12
Premises, equipment, and calibration	10
Segregation of unsaleable goods	9
General transportation and delivery	7
Housekeeping and pest control	6

Although numerous regulatory references to stability exist, only those that focus on the distribution of drug products are addressed in this article. For example, ICH's "Q1A: Stability Testing of New Drug Substances and Products," states that data from accelerated stability studies can be used to evaluate the effect of short-term excursions higher or lower than label storage conditions that may occur during the shipping of drug products. If a significant change occurs during the accelerated stability study, additional testing at the intermediate storage condition should be conducted (2).

The 1998 FDA draft guidance for stability testing recommends the use of thermal cycling studies to examine the effects of temperature variation on drug products. Packaged drug products are cycled through the temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution. The product is cycled from high to low temperatures for several days and the exposure is repeated several times (e.g., 3 cycles) (1).

USP (26) recommends that if no specific storage directions or limitations are provided in the individual monograph but the label provides a storage temperature on the basis of stability data, then the product storage label applies (e.g., freezer, cold, cool, controlled room temperature). The guidance states, "An article for which storage at controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label." Products having no specific storage directions or limitations in the monograph, should be stored and distributed with protection from moisture, freezing, and excessive heat (5).

In contrast to the US requirements, the Committee for Proprietary Medicinal Products recently released an updated guidance that does not require a labeling statement on products with stability data at 25 °C and 60% RH (6). Although the regulations do not provide requirements for running stability distribution studies for the shipment of pharmaceutical products per se, regulatory agencies expect the manufacturer to understand its product's stability profile thoroughly and to maintain control during the distribution process.

In recent years, pharmaceutical companies have been asked

**Table II: Long-term stability study.**

Storage condition	Testing condition
Controlled room temperature 20–25 °C	25 °C and 60% RH for 12 months
Refrigerated condition 2–8 °C	5 °C for 12 months
Freezer condition –20 to –10 °C	–20 °C for 12 months

**Table III: Accelerated stability study.**

Storage condition	Testing condition
Controlled room temperature 20–25 °C	40 °C and 75% RH for 6 months
Refrigerated condition 2–8 °C	25 °C and 60% RH for 6 months
Freezer condition –20 to –10 °C	5 °C for 6 months

to respond to regulatory agency questions regarding company- and product-specific distribution practices. The following are examples of recent 483 citations (7).

- August 1998: Standard operating procedures do not describe how kits are packaged or labeled to ensure that temperature specifications are maintained during shipment.
- January 1999: No records are available to ensure that products are shipped and maintained within their storage temperature requirements.
- 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.
- May 1999: The standard operating procedure lacks an acceptance criteria for the storage and movement of material between two sites.
- January 2000: Temperature specifications are not defined for the shipment of packaged, temperature-monitored bulk products and filled vials to and from the filling contractor.
- June 2000: No documentation exists for requesting or approving the transportation study of capped tablets following a lot rework. Quality assurance does not approve the "Standard Practice for Performance Testing of Shipping Containers and Systems" procedure.
- October 2001: Bulk material intended for refrigerated storage is left at ambient conditions for several days before shipping.
- March 2003: The shipment by truck of finished vials from one site to another is not yet validated.

Furthermore, at a recent USP Open Conference meeting on packaging, storage, and distribution, a speaker from the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) described his country's recent experience with the enforcement of good shipping and distribution practices. The MHRA has dedicated inspectors who focus solely on this area. Table I summarizes inspection results from 2002 (8).

**Table IV: Short-term temperature excursion study.**

Storage condition	Testing condition
Controlled room temperature 20–25 °C	1) –20 °C for 2 days 2) 60 °C and 75% RH for 2 days
Refrigerated condition 2–8 °C	1) –20 °C for 2 days 2) 40 °C and 75% RH for 2 days
Freezer condition –20 to –10 °C	1) 25 °C and 60% RH for 2 days

Note: Alternative study designs may be used when results from development stress studies indicate that a product is unstable at specific extreme temperatures (e.g., if stress studies show a product is unstable at 60 °C, a short-term temperature excursion study at 50 °C may be more appropriate. If upon freezing the physical properties of a protein are altered, a 0–2 °C short-term temperature excursion study may be more appropriate).

### Key principle

The complexity of the pharmaceutical supply chain requires an understanding of the interdependency between related processes and product characteristics. Company personnel (e.g., stability experts, distribution personnel) must share information. Pharmaceutical products should be shipped in a manner that ensures products will not be adversely affected by environmental conditions on the basis of product stability, product history, packaging information, and the transport system used.

**Table V: Thermal cycling excursion study.**

Storage condition	Testing condition*
Controlled room temperature 20–25 °C	–20 °C for 2 days followed by 40 °C and 75% RH for 2 days
Refrigerated condition 2–8 °C	–20 °C for 2 days followed by 25 °C and 60% RH for 2 days
Freezer condition –20 to –10 °C	–20 °C for 2 days followed by 5 °C for 2 days

\* All testing conditions are repeated for a total of three cycles.

The pharmaceutical industry and regulatory agencies recognize that drug products may be subjected to short-term temperature excursions during the transportation process. A stability program to support the effect of temperature excursions during the distribution of medicinal drug products on product quality is outlined.

**Study strategy.** Drug products will be exposed to temperature conditions both inside and outside of label storage conditions. Long-term and accelerated stability studies will be completed per ICH guidelines. The following distribution stability studies will be initiated when stability profiles indicate the need for additional data:

- long-term stability study per ICH Q1A (see Table II)
- accelerated stability study per ICH Q1A (see Table III)

**Table VI: Analytical data for a refrigerated product.**

Product group X	Item code	Description (mg)	Storage condition	Routine 5 °C (M)	Accelerated	Excursions	Excursions	Excursions cycling*	Comments**
					25 °C and 60%	20 °C	40 °C and 75%		
					(months)	(days)	(days)		
Vials	VL123	5	Refrigerated	24	6	2	2	Cycling*	Shipping study Y reports
Vials	VL456	10	Refrigerated	24	6	—	—	—	—
Vials	VL789	20	Refrigerated	24	6	2	2	Cycling*	Shipping study Z reports

\* -20 °C for 2 days followed by 25 °C and 60% RH for 2 days. Repeat for a total of three cycles.

\*\* The shipping report written from excursion test results and information about the report location is referenced in the comments section.

Item Code(s): Wabc  
Recommended storage condition: refrigerated

**Shipping Criteria:**

Temperature ranges	Time
$\leq -20\text{ }^\circ\text{C}$	avoid
$-20\text{ to }2\text{ }^\circ\text{C}$	2 d
$2\text{--}8\text{ }^\circ\text{C}$	until expiry
$8\text{--}25\text{ }^\circ\text{C}$	6 d
$25\text{--}40\text{ }^\circ\text{C}$	2 d
$>40\text{ }^\circ\text{C}$	avoid

Controlled: Shipping study Y report  
Shipping study Z report

**Figure 1:** A shipping and distribution control strategy for product X.

- short-term temperature excursion study: to be designed by anticipating the extreme high and low temperature conditions that may occur during drug product shipment on the basis of the drug product's known properties, which have been obtained through the development phase study (see Table IV)
- thermal cycling excursion study: to be designed by anticipating which fluctuating environmental conditions may occur during drug product distribution (see Table V).

**Study design.** Short-term temperature excursion and thermal cycling excursion studies are one-time studies. These studies are run on the final formulation in the marketed package. If the formulation or primary package changes, these studies should be repeated, unless otherwise scientifically justified.

Studies should be run on one or more batches of a drug product. The study will be designed on the basis of storage classifications per USP recommendation: controlled room temperature, cool, refrigerated (i.e., cold), and frozen (i.e., freezer). As recommended in the ICH Guideline Q1D, bracketing may be used (9).

Anticipating the extreme temperature conditions would determine how studies should be developed. Upon the comple-

tion of the shipping study, samples will be subject to long-term stability testing conditions to verify that the exposed product meets shelf-life requirements.

**Extreme temperature conditions.** Stability studies will be developed by anticipating stressful environmental conditions. This approach demonstrates a higher or lower temperature excursion than what is expected to occur during the routine distribution of a product.

**Analytical testing.** Studies will evaluate the effect of chemical (e.g., potency, related substances) and physical (e.g., dissolution, particulates, and physical appearance including primary packaging) properties of the drug products. Test results must meet appropriate specifications using validated stability indicating methods. ICH definitions may be used to define significant changes (2). Studies may also evaluate container-closure integrity for products.

**Out-of-specification results.** If a significant change occurs, short-term temperature and/or thermal cycling excursion studies may be repeated using less stressful conditions. Samples pulled at intermediate time-points should be tested to determine the maximum allowable temperature excursion and/or time range. Results may indicate the need for distribution areas to implement product protective shipping methods (e.g., expedite shipping, qualified packaging).

**Data analysis.** Combining stability data from long-term, accelerated, short-term temperature, and thermal cycling excursion studies will provide the information needed to predict the effect of temperature excursions on drug product quality during distribution (see Table VI). Data at each time-point must pass stated analytical requirements (i.e., meets all specifications).

Shipping study results can be used to write shipping and distribution control strategy documents (see Figure 1). The advantages of a shipping and distribution control strategy document are as follows: records acceptable transit time limits and temperature ranges; implements a high-level approach that will prompt investigations; and provides process control for shipping a product. Such a stability program will increase the success of a pharmaceutical manufacturer's distribution process.

## Summary

The effect of temperature excursions, outside of labeled storage conditions, can be evaluated on the basis of the stability analysis for that drug. Because the distribution environment is

highly variable, a stability program should be established that provides stability profiles for each product. This article describes a stability program strategy designed on the basis of the information provided by the development and routine ICH Q1A stability programs. In essence, the protocols for the distribution stability program would then be developed by understanding product characteristics, typical environmental conditions, and anticipating environmental extremes. The combined data would then provide the information necessary to develop product-specific shipping criteria. The latter would be used to design a shipping document (i.e., shipping and distribution control strategy document) that complements the overall robustness of a distribution program.

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