

Technical Report No. 53  
Guidance for Industry:  
Stability Testing to  
Support Distribution of  
New Drug Products



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## **PDA Stability Testing to Support Distribution of New Drug Products**

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# **Guidance for Industry: Stability Testing to Support Distribution of New Drug Products**

**Technical Report No. 53**

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## 1.0 Introduction

Stability testing is the primary type of testing necessary to provide data that will enable appropriate decisions regarding the conditions under which a finished material is to be stored, transported, and used. The International Conference on Harmonisation (ICH) published guidelines that address storage conditions, whereas this PDA Technical Report addresses stability studies to support distribution conditions. Shock and vibration testing also has a role, particularly in regard to transportation of liquid formulations of certain biologic molecules. This guidance will provide recommendations on the stability studies needed address the risks that face drug products in the distribution process, as well as supporting temperature excursions outside the long-term storage condition during storage.

This guidance focuses on four situations that should be considered during stability testing; these are:

1. **Product Storage:** Temperature is typically controlled and the risk of shock and vibration is expected to be minimal.
2. **Manufacturing and distribution operations (road, sea, and/or air):** Product is moved from one storage condition to another: temperature control may or may not be present. In addition to temperature stress, the risk of shock and vibration may be significant during distribution operations.
3. **Product Use under many circumstances, including following reconstitution from powder or simply by end-users (practitioners and/or patients):** There may be considerable variability in temperature control but the risk of shock and vibration is minimal.
4. **Excursions:** Temperature goes outside the recommended range for that segment of distribution or during controlled temperature storage of the product.

For products stored under frozen or refrigerated long-term conditions in situations 2 and 3 above, product may be exposed to temperature conditions outside the long-term storage condition during manufacturing, distribution and customer handling steps (e.g., bulk transport, filling and packaging operations, final product distribution operations, end user administration). The allowable exposure period and temperature range outside of the long-term storage condition is determined by accelerated stability data and can be further supported with the use of temperature stress and temperature-cycling stability data. When there is not a significant difference between long-term and accelerated stability study results, the allowable exposure period and temperature may be defined by the accelerated stability study (e.g., 6 months at 25°C for a 2-8°C product). However, if there is a significant difference in the stability data obtained between accelerated and long-term conditions, a shorter exposure period may need to be established based upon cumulative long-term and accelerated losses and meeting the required shelf life specifications. For products with limited exposure periods outside of the long-term storage conditions, tracking and control of product exposure periods becomes essential at each step of the process and distribution chain.

The allowable time and temperature conditions outside of the long-term storage condition for a material must be budgeted among competing needs such as additional manufacturing or packaging and labeling operations, transportation and the end user. This has been referred to as "time out of refrigeration," "time out of storage," or "time out of temperature." For the purpose of this guidance, the phrase "time out of storage" will be used.

For situation 4, to support excursions that go beyond accelerated conditions or have a longer duration, additional studies above the accelerated conditions, freeze-thaw studies and temperature-cycling studies may be useful.

This guidance will also address the frequency, timing and extent of stability and shock and vibration testing needed to provide adequate support for appropriate label statements and to cover the four situations described above.

It is recommended that stability studies be designed and conducted with consideration to the expected shipment durations, the predicted temperature exposure ranges and times out of storage that the product will experience during manufacturing, packaging, transport and distribution, especially where these data exist or are available.

## 1.1 Purpose

The objective of this document is to describe and justify the studies using scientific data and rationale necessary to determine an appropriate stability budget for a drug product. This is the first of seven categories, or pillars, of Good Distribution Practices (GDPs), depicted in **Table 1.1**, below.

Each product should be evaluated against the pillars of GDPs to identify the individual categories that apply within each pillar. PDA has provided general guidance on the first four in *Technical Report No. 52: Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain*, published in 2011, and will provide specific guidance in Technical Reports on Qualification/Validation, Continuous Improvement, and Import/Export Compliance, which are under development.

**Table 1.1 Good Distribution Practices Pillars; this Technical Report addresses the first pillar**

Stability	Distribution Control Management	Performance Management	Supplier Chain Partner Management	Qualification/Validation	Continuous Improvement	Import/Export Compliance
Storage Temperature	Qualification and Training of Personnel	Performance Measurement and Reporting	Partner Selection	Ambient Temperature Profiles	Industry Trends	Customs Release
Shipping Temperatures	Premises and Equipment	Self Inspections	Quality Audit	Passive Shipping Systems	Regulatory Trends	Documentation Control
Stability Testing to Support Distribution	Material Handling	Management Review Meetings	Quality Agreements	Active Shipping	Requalification	Product Tracking
	Storage and Inventory Control		Business Review Meetings	Facility Qualification		
	Transportation			Warehouse Management System Validation		
	Product Disposition and Distribution			Distribution Validation Master Plans		
	Product Protection					
	Returns Management					
	Exception Management					

A stability budget considers the results of long-term, accelerated, extreme excursion, and temperature-cycling studies to determine the amount of time out of storage that a drug product may experience without any significant risk to its quality. Firms have used the idea of a stability budget to assign permissible time out of storage for packaging and labeling operations for refrigerated drug products for some time. This concept has been expanded in the present document to include storage and distribution as well. It is intended to complement existing guidance on stability studies and maintaining the quality of pharmaceuticals during distribution (1, 2). The studies and recommendations provided in this document are by no means mandatory, but represent a consensus of current industry best practices.

## 1.2 Scope

This technical report is intended to cover new drug products. The principles described may also be applied to other finished materials such as drug substances, finished drug product held in bulk before final packaging, and clinical trial materials that may be stored for significant periods of time and are also subject to the risks of distribution. All drug products are intended to be covered by this guidance, including small molecules, biologic and biotechnology-derived materials, vaccines, and radiopharmaceuticals. While each drug product may have particular considerations, it is nevertheless the case that all face the same risks to quality as they go through the distribution process. This document is intended to cover new materials, but the principles described may be applied to existing ones should firms choose to do so.

Intermediates and excipients are not in the scope of this guidance because they are not finished materials and are subject to further processing other than packaging.