

<b>Title: Assessment of Shipping Processes for Drug Products (DP)</b>					
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## Introduction

This document provides guidance on assessing the transportation of Drug Products (DP). It can be applied to assessment of shipping Bulk DP and finished commercially packaged DP (finished product+) between any two locations . such as manufacturing sites, wholesale distribution centres, and receiving sites or . within the GMP sites distribution network.

The practices described here are intended to evaluate the risks to the quality of the materials being shipped and are endorsed by subject matter experts.

DPs should be transported in a manner that assures the maintenance of product quality and this guidance provides recommendations for assessing the shipping conditions used in order to document how this assurance is achieved. Awareness of worst-case conditions, the potential for unexpected delays and product stability knowledge, for example, are among key inputs to understanding the potential for risk to product quality from shipping. Where the risk to product quality is significant, qualification of the chosen shipping process may be appropriate.

This guidance is intended to complement and supplement guidance available elsewhere on the topic of shipping of Drug Products. It does not address design considerations for a shipping process, such as selection of shipping containers or packing materials, planning for handling of materials, or selection of transportation routes. It is also not intended to address needs for shipping of vaccines and biopharmaceutical products, which may have additional regulatory requirements and for which some other guidance exists.

Documented assessments that include evaluation of risks to DP quality from shipping may be used as the foundation for approaching local authorities with requests to eliminate local receipt testing. These assessments may in some cases be sufficient to eliminate the need for documented qualification of shipping processes.

## Recommendations and Rationale

Shipping of DP can expose the material to conditions that may put product quality at risk. For products known to be sensitive to shipping conditions, a Shipping Qualification (SQ) study should be performed.

A documented risk assessment (for more robust products) or risk assessment plus completed SQ study (for more sensitive products) will provide scientifically-based justification that the risks have been considered and that, when warranted, risks posed from shipping the DP have been appropriately mitigated. An additional benefit provided by this documented information is that local receipt testing of the DP by the receiving site, should not be necessary from a quality control or quality assurance perspective.

In general, regulatory guidance (e.g. from ICH, FDA, EMEA) do not require that SQ be performed in all cases, although some organizations have published recommendations for SQ. For more robust products (i.e., less environmentally sensitive, more stable products) where the risk assessment indicates that shipping does not pose significant risk to product quality, an SQ study is not a value-added activity and the risk assessment is by itself sufficient documented information to establish that we have evaluated the shipping process for that product.

## A. Product Stability Data

Knowledge of product stability is a key part of understanding the risk to product quality from the shipping process. Information about product stability can come from several sources, such as:

- “ Regulatory filing for a formulated DP;
- “ Routine, annual stability testing requirements
- “ Accelerated stability challenges, where the conditions used for accelerated stability testing may in some cases approximate expected worst-case limits of variability of environmental conditions approached during some phases of transit;
- “ Short-term stability data, temperature excursion incident investigations, temperature studies performed under manufacturing conditions, freeze/thaw and/or temperature cycling studies;
- “ Test data collected from before and after shipping and information on environmental conditions encountered during transit; and/or
- “ Other relevant studies such as shipping of research materials that may have been performed during product development and could have been documented as part of an earlier research (IND) regulatory filing. Performance differences in packing and other protective materials that may be used should be understood.

## B. Transit Conditions

DPs are transported in a commercial environment that can be considerably different than the controlled manufacturing and static storage environments. Shipping conditions such as unforeseen transport events (such as delays), temporary storage in uncontrolled environments while awaiting the next stage of transportation, and variations in weather can expose product to conditions outside the long-term storage conditions established with the product registration.

Worst case conditions that could be encountered, together with what is known about the susceptibility of the DP to adverse conditions, should be considered in an assessment of shipping risks. Without controls, environmental conditions encountered during transit could be more severe than those experienced during normal storage.

Environmental variations to which the product may be exposed include conditions at origin, destination, transportation hubs and throughout the transit route. Environmental profiles should be based on realistic expectations of transport conditions, developed using scientifically sound criteria. This may be done in various ways such as using review of historic data, review of published standards, or field-testing/monitoring of actual shipments including seasonal variations. Profiles should include anticipated extreme conditions that challenge the effectiveness of controlling temperature, exposure to moisture, prevention of oxidation, etc. as appropriate, with the packaging to be used.

Transportation conditions can pose several potential threats to product quality. Among the potential threats are:

- “ Temperature variation;
- “ Physical agitation, including vibration, shock and compression;
- “ Variable pressures, experienced by products shipped by air transport;
- “ Exposure to light;
- “ Variation in humidity (for susceptible DPs, this is typically mitigated by primary packaging).

Temperature variations can result from seasonal effects, transport routes (ground, air, land and sea transport) and potential stopover points. Considerations should include the range of temperatures that can be experienced and estimation of the duration of exposure to potentially adverse conditions. Several points to consider regarding temperature variations, including potential effects from use of ancillary packaging systems, are described in another guidance.

- “ Ancillary packaging components/systems are means used in combination with tertiary packaging to maintain the required temperature during transit, e.g. passive systems such as insulated containers with or without refrigerants and active systems such as refrigerated trucks.

#### **D. Perform Risk Assessment**

A Quality Risk Management guideline or basis for performing a risk assessment on a shipping process is provided in Appendix 1. It includes several risk questions about impacts or the potential impacts of shipping conditions on different aspects of DP quality.

#### **E. Shipping Qualification**

Qualification is documented testing that shows with a high degree of assurance that a specific process will meet pre-determined acceptance criteria, in contrast to validation which also achieves that but additionally involves testing that is performed under highly controlled conditions to demonstrate process consistency. Transportation processes can thus be qualified, rather than validated, as it is not possible to control all the parameters that could affect the transportation process (e.g. weather, customs and traffic delays, etc.), so the term shipping qualification is used here.

Where risk assessment indicates that shipping the bulk DP or finished DP can pose a risk to product quality, qualification of the shipping process is recommended. This involves conducting a study using a pre-approved protocol that identifies shipping parameters and protective measures to mitigate risks, establishes acceptance criteria and specifies the testing to be performed. It may include use of data loggers or monitors to assist in monitoring environmental conditions such as temperature and humidity experienced during transit.

Shipping qualification should only be applied where:

- “ There is a particular product sensitivity or instability that could result in patient injury or result in product that is unfit for use, etc.;
- “ Insufficient information is available about the risk to product quality from transit conditions and import testing is not conducted; or
- “ A cost benefit analysis favors shipping qualification as a means of reducing overall costs and/or speed of delivery to market.

Typical components of a SQ protocol are described in other reference guidance. Examples of SQ protocols are available. Protocols may have different points of focus, depending on the product being studied, so it is helpful to review more than one to see examples of features that may be useful for a planned qualification study.

Acceptance criteria for the SQ should be provided that address the risks and risk management identified in the risk assessment. Testing performed for SQ studies should use the actual finished product or bulk DP that is to be shipped. The packaging components used for the SQ studies should be representative of components to be regularly used for shipping. Testing may be performed using temperature-controlled environments to reflect expected conditions.

When used, calibrated temperature data loggers should be placed close to product (that is, inside insulated or temperature-controlled packaging with the product) to collect accurate data that indicates temperatures that the DP experiences in transit. Enough positions should be monitored to get representative data on variations that may be inherent in load packing, load configuration, or manner of transport.

Shipping and receiving sites should coordinate activities in preparing for an SQ study, as both sites have essential responsibilities for ensuring successful preparation and execution of these studies.

## Appendix I: Basis for a Risk Assessment on Determining the need for a Shipping Qualification

### 1. INTRODUCTION AND OBJECTIVE

This appendix is aimed at providing risk-based guidance on when shipping qualification should be applied. A completed, product specific risk assessment can also be employed as part of the supporting documentation package to justify the choice of shipping process and that receipt testing is not value adding (if appropriate).

The risk question for this exercise is – “Which product-specific Critical Quality Attributes are at risk of adverse impact under conditions proposed for the intended shipping method and that without SQ would justify product re-testing upon receipt/importation?”

The critical quality attributes of some products (APIs and DPs) are sensitive to impairment during shipping. The physical form of the product is a key factor, but of greater significance is how well controlled the transportation and intermediate storage conditions are during the shipping process. Impairment can come in the form of degradation, microbiological proliferation, moisture absorption, particle size stratification and dosage form breakage to name but a few. The integrity of packaging may also be compromised in some instances.

The maintenance of product quality during shipment can be assured by a number of mitigating factors – including, but not limited to:

- Product design (e.g., inherent stability or dosage form robustness)
- Packaging design/qualification (e.g. light, oxygen and/or moisture excluding, shock absorbing, tamper evident etc)
- Labeling
- Partnering and contractual arrangements
- Supplier (shipper) audit and/or qualification
- Cold chain transport and storage
- Data logging during transport
- Limited duration transport or special transportation arrangements
- Enhanced short-term stability study
- Receipt testing
- Shipping qualification

In addition to this, should a problem be found upon receipt of goods, then quality systems such as ‘notification of damaged goods’ will be used to prompt an

### 3.6 Risk Ranking Matrix

