Regulatory Basis:
FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

General Discussion

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.

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.

SQ may be expected by local authorities in some countries even if a risk assessment is performed and concludes that SQ is not necessary. SQ performed in such cases will be additional verification that transit conditions do not pose significant risk to product quality, in turn supporting requests for the cessation of receipt testing. However, in some cases authorities may still insist on local receipt testing regardless of the evidence provided.

- Secondary components generally serve to identify, protect, market and communicate information about the product, e.g. labels, leaflets, fiber drums, cartons and boxes. These components influence the loads that can be placed within the transportation container (tertiary package) and determine the number of primary packaging components that can be held. Secondary components generally are not designed to afford any protection of the product from adverse environmental conditions.

- Tertiary packaging components are used to assemble primary and secondary packages into forms of the basic transportation unit, such as but not only corrugated cardboard boxes and plastic shrink wrapping. They provide some protection against mechanical impact and may also provide insulation for thermal protection.
- 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.

Appendix 1: 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

3.7 Risk Ranking and Filtering

Potential Risks		Risk Analysis			Overall Score
		Probability	Severity	Detection	
1	What is the risk of significantly reducing product potency due to temperature, humidity, light or pressure variations during the shipping process?				
Comments					
2	What is risk of generating significant degradation related impurities due to temperature, humidity, light or pressure variations during the shipping process?				
Comments					
3	What is the risk of microbiological proliferation within the product as a result of the shipping process?				
Comments					
4	What is the risk of particle size stratification within bulk product due to agitation during the shipping process?				
Comments					
5	What is the risk of powder separation within bulk product due to vibration during the shipping process?				
Comments					
6	What is the risk of dosage form damage/breakage due to vibration or shock effects during the shipping process?				
Comments					
7	What is the risk of being out of compliance with Regulations or market authorizations associated with the receiving site/country should shipping qualification not be conducted?				
Comments					

4. RISK ASSESSMENT SUMMARY AND OUTCOME

