Guidance for the development of insulated shipping containers to ensure the quality of products, which have registered storage conditions between 2° and 8° Celsius.

Table of Contents

1. Background and current situation…..……3
2. Purpose and benefits…….. 4
3. Scope……4
4. Definition and abbreviations……..4
4.1 Insulated shipping container…… 4
4.2 Pharmaceutical company…….. 4
4.3 Supplier……5
4.4 Distributor……5
4.5 Qualification laboratory…….. 5
4.6 Third Party……5
4.7 Representative product / product group……..5
4.8 System……..5
4.9 Preloading…… 5
4.10 Qualification…… 5
4.11 Cold chain…… 5
4.12 Cooling elements…… 5
5. Responsibility……..……..6
5.1 Pharmaceutical license holder…… 6
5.2 Technical agreement…… 6
6. Quality system……..……6
7. Development recommendations……..6
7.1 Container……..6
7.2 Cooling elements…… 7
8. Shipping container qualification……..……7
8.1 List of product groups……7
8.2 Qualification documents to be used in the protocol…….. 8
8.3 Testing and temperature profiles to be used…… 9
8.4 Further documents to be applied…… 9
9. Reference documents……..10
10. Appendix A……11

1 Background & Current Situation

Products with registered storage conditions between 2° and 8° C must be transported using a system to ensure the quality of the product.

Pharmaceutical products that are temperature sensitive and that stay outside the recommended range might impact patient safety due to product alterations. This deterioration in product quality and patient safety can lead to a withdrawal of the product and thus to product loss. It can also lead to Company liability when doubts are raised with regard to product quality and safety following temperature deviations.

In order to meet their obligation to ensure the maximum quality and thus safety of their products, most pharmaceutical companies have their own standards and procedures on how to handle their finished products that are registered for storage between 2° and 8° C. And every **pharmaceutical company** imposes these procedures on their organization or their respective service providers.

Many pharmaceutical companies today are developing – together with **suppliers** – individual shipping containers and configurations for the products of their **cold chain**.

As a result, there:

- are lots of different solutions on the market;
- is a lot of effort and money spent for the development and purchase of these individual solutions;
- needs to be multiple qualification efforts for every new container instead of being able use existing shipping containers (that have already been tested and are on the market);
- is no flexibility in usage.

Different players in the supply chain (pharmaceutical manufacturers, wholesalers, service providers, etc.) are obliged to entertain multiple systems tailored to different customer groups, thus increasing cost and the possibility of errors.

2 Purpose & Benefits

The purpose of this document is to provide guidance for the development or comparison of, shipping containers for **cold chain** pharmaceutical products including, but not limited to, such considerations as:

- minimum requirements for container qualification;
- temperature profiles for container qualification.

These documents are intended for use by any party involved in the development of shipping containers for **cold chain** pharmaceutical products including, but not limited to:

- **suppliers** and manufacturers of such containers;
- pharmaceutical companies involved in the specification and/or development and/or testing of such containers;
- third parties involved in the development or testing of such containers (e.g. laboratories).

These documents are not intended to be all encompassing and should be considered as a general starting point for container development and thermal analysis.

The expected benefits of adherence to these documents are:

- improved product integrity and patient safety;
- increased cost effectiveness by:
  - decreasing the potential to lose product and/or for company liability;
  - avoiding duplication of effort and reducing risk of failure.

3 Scope

This document is valid for pharmaceutical finished goods for which the registration states a storage condition between 2° and 8° C. The document covers minimum requirements for insulated shipping containers with passive cooling and considers qualification for either 48 or 96 hours.

4 Definitions and Abbreviations

4.1 Insulated shipping container:
Insulated outer box used for transport.

4.2 Pharmaceutical company:
The party with responsibility for distributing pharmaceutical products in the marketplace.

4.3 Supplier:
Manufacturer of shipping containers.

4.4 Distributor:
Party providing logistic services such as transport/delivery and/or warehousing. The Distributor may, in some cases, be the **Pharmaceutical Company**.

4.5 Qualification laboratory:
Party providing services for the testing and validation of shipping containers. May be a **third party**.

4.6 Third Party:
A party other than the **supplier** or the **pharmaceutical company**.

4.7 Representative Product/Product Group:
Product presentations with similar thermal characteristics for which the same test requirements can be used and, therefore, for which one shipping container can be developed.

4.8 System:
A collective term for an insulated shipping container and its components, comprising:
- insulated box;
- **cooling element**s with their specific predefined configuration;
- filling material;
- specific, or similar and representative, product.

4.9 Preloading:
Placing of product into a system without the **cooling element**s in such a way that the other system components can be added at a later stage (e.g. immediately before shipment) without having to remove the product.

4.10 Qualification:
Documented testing that demonstrates with a high degree of assurance that a specific system will meet the pre-determined acceptance criteria.

4.11 Cold Chain:
An uninterrupted series of storage and distribution activities which maintains a given temperature range, e.g. between 2° and 8° C.

4.12 Cooling element:
Part of a shipping system, which is designed to reduce the temperature of the surrounding environment by absorbing heat.

5 Responsibility

5.1 The overall responsibility for the development of **insulated shipping containers** is with the pharmaceutical license holder.

5.2 There should be a technical agreement between the **pharmaceutical company** and any third parties.

6 Quality System

All **suppliers** and **qualification laboratories** used must have a quality system in place.

7 Development Recommendations

In order to develop containers, a number of factors should be considered, including, but not limited to:

7.1 Container

It is recommended that the following points be considered when starting the development of a container:

If applicable:

- Temperature profiles used for qualifying the container should be based on the assumption that no dry ice or active coolant will be used;
- The outer carton should be replaceable;
- The inner part of the container should be sufficiently robust to be re-usable;
- Handling/Assembly should be as simple as possible;
- Recycling should be supported in line with local environmental regulations;
- Materials used should be environmentally friendly;
- **Preloading** of the container should be possible;
- A modular system should be used: the container should have footprint dimensions of 1200x800 mm or designed such that the cartons can be assembled to fit to the pallet size (½, ¼, 1/8 etc.)
  or equivalent for US-pallets (48”x48” or 48”x40”);
- Manual handling or handling with a fork-lift should be possible;
- The height of the container should be determined in view of the type of transport route to be used (e.g. maximum 800mm (including pallet height) for some intra-European air transport).

A **supplier**'s description of a developed box should include, as a minimum, the following:

- Internal dimensions (i.e. space available for product);
- External dimensions;
- Material specifications of all components;
- Weight and dimensions of all individual components and also of the total system.

7.2 Cooling Elements

When selecting a type of **cooling element** to be used in any configuration, the following aspects should be taken into consideration. The impact is greater if the scope of the distribution network widens:

- Use of **cooling element**s pre-cooled at 5°C or -18°C or any combination of these;
- Quality of the **cooling elements** with respect to being 'leak proof';
- Non-toxic and non-hazardous;
- Requirements for waste handling;
- Re-use and/or recycling.

The type of pre-cooling required should be incorporated in the qualification protocol.

8 Shipping Container Qualification

8.1 List of product groups

Pharmaceutical companies may distribute many different products with similar thermal characteristics (e.g. mass, specific heat, air/product ratio etc.). The following classification may be used to define similar and **representative** products:

- creams;
- aqueous solutions;
- lyophilized products;
- powders;
- syrups;
- others.

A rationale should be provided enabling a specific **qualification** to be used to approve shipments of different products using the same container and configuration. This rationale should explore the impact of the following characteristics:

- ratio air/product;
- thermal mass (i.e. specific heat capacity);
- different minimum load and maximum load when shipping different products.

8.2 Qualification documents to be used in a qualification protocol

8.2.1 Prior to defining an explicit **qualification** protocol a temperature mapping should be conducted on the developed container. This will define the different positions of the thermocouples to be used during the tests. During the tests, thermocouples must also be placed in the “cold spot” and “hot spot” identified during the temperature mapping.

8.2.2 The qualification has to be performed on the whole system being:
- insulated box;
- **cooling elements** with their specific predefined configuration;
- filling material;
- specific, or similar and **representative**, product.

8.2.3 Reproducibility has to be demonstrated by conducting a minimum of 3 tests of each combination (of the whole system and temperature profile). Simulated testing can be conducted in the laboratory using 3 different containers at the same time. Field-testing may be performed using real shipments.

8.2.4 The **qualification** protocol will be agreed upon and signed off by all parties (being **Pharmaceutical company** and/or **Distributor** and **Qualification Laboratory**) involved in the distribution process of the product.

8.2.5 The **qualification** process should be at all times linked with the product temperature. This can be solved by imposing one of the following:
- the thermocouples are inserted in to the product or its placebo;
- if this is impossible, a study should be performed with respect to the correlation of the product temperature and the primary packaging temperature. Based on this, the container **qualification** can be performed by positioning the thermocouples on the primary packaging.

8.2.6 The following topics should be covered in the **qualification** protocol:
- definition of all parties involved;
- definition of the **system**;
- minimum and Maximum load;
- scope of the distribution channel where the container will be used:
  - national/international;
  - intra or inter-continental;
  - seasons.

8.2.7 Product Scope and/or Rationale for shipping other products using the same **system.**

8.2.8 Detailed description of tests, including:
- temperature profile(s);
- frequency of tests;
- positioning of thermocouples;
- specification of measurement equipment.

8.2.9 Possible use of field testing (monitoring of real shipments) as the basis for a PQ.

8.2.10 Acceptance criteria.

8.3 Testing & Temperature Profiles to be used

The criterion used for all qualification tests is that the internal product temperature must stay within the targeted temperature range for the entire duration of all tests.

8.3.1 Selecting a Temperature Profile

When defining a temperature profile to be used for qualification testing consider the following:
- database study: data is publicly available providing regional, national or world wide daily temperature measurements. This data should be analyzed with respect to the logistics routes to be employed;
- focused simulation tests: monitoring air temperature (using a temperature recording device on the outside of the shipping containers) during shipments through a specific distribution system enables the development of realistic temperature profiles.

8.3.2 Types of Test to be conducted

Appendix A gives an example of possible test types that could be used for **qualification** testing for different scenarios of climatic conditions / logistics routes.

Instead of using the temperature profiles in the Appendix, it is also possible to develop alternative profiles based on temperature data collected for a specific transport scenario (for example data collected by monitoring air temperatures during transport on a particular route).

In all cases, data may be recorded until the product internal temperature shows an excursion outside of the targeted temperature range.

8.4 Further documents to be applied

ASTM Standards (http://www.astm.com)

IATA Dangerous Goods Regulations (Packaging)

9 Reference Documents

- Guidelines on good distribution practice of medicinal products for human use 94/C 63/03
- WHO-guide to good storage practices for pharmaceuticals
- Commission Directive 91/356/EEC
- WHO technical report series, No.908, 2003 Annex 9
- EU Directive 2001/83/EC
- ISTA Resource cook 2002 7D

10 Appendix A

This Appendix gives an example of possible test types that could be used for qualification testing for different scenarios of climatic conditions / logistics routes.

Shipping from \ Shipping to	Mild Summer	Summer	Mild Winter	Winter
Mild Summer	1	2	5	7
Summer	2	2	6	8
Mild Winter	5	6	3	4
Winter	7	8	4	4

Test Types (Scenario)

In this example, cyclic and (if possible) constant temperature tests should be performed. The details of these tests are given in the table below. In this example, these tests are, in each case, for a 48-hour qualification. By repeating the tests without interruption, the same tests could be used for periods which are multiples of 48 hours.

The profiles are theoretically defined in order to simulate a capacity of an insulated box.

Test Type (Scenario)	Constant Temperature Test		Cyclic Test
	External Temperature	Duration	
1 (Mild Summer to Mild Summer)	20°C	48 hours	12 hrs at 20°C, then 6 hrs at 40°C, then 12 hrs at 20°C, then 6 hrs at 40°C, then 12 hrs at 20°C.
2 (Mild Summer to Summer) or (Summer to Mild Summer) or (Summer to Summer)	20°C	48 hours	12 hrs at 25°C, then 6 hrs at 45°C, then 12 hrs at 25°C, then 6 hrs at 45°C, then 12 hrs at 25°C.
3 (Mild Winter to Mild Winter)	20°C	48 hours	12 hrs at 20°C, then 4 hrs at -5°C, then 12 hrs at 20°C, then 4 hrs at -5°C, then 16 hrs at 20°C.
4 (Mild Winter to Winter) or (Winter to Mild Winter) or (Winter to Winter)	20°C	48 hours	12 hrs at 20°C, then 4 hrs at -10°C, then 12 hrs at 20°C, then 4 hrs at -10°C, then 16 hrs at 20°C.
5 (Mild Winter to Mild Summer) or (Mild Summer to Mild Winter)	20°C	48 hours	12 hrs at 20°C, then 4 hrs at -5°C, then 12 hrs at 20°C, then 6 hrs at 40°C, then 14 hrs at 20°C
6 (Summer to Mild Winter) or (Mild Winter to Summer)	25°C	48 hours	12 hrs at 25°C, then 4 hrs at -5°C, then 12 hrs at 20°C, then 6 hrs at 45°C, then 14 hrs at 25°C
7 (Winter to Mild Summer) or (Mild Summer to Winter)	20°c	48 hours	12 hrs at 20°C, then 4 hrs at -10°C, then 12 hrs at 20°C, then 6 hrs at 40°C, then 14 hrs at 20°C
8 (Winter to Summer) or (Summer to Winter)	25°C	48 hours	12 hrs at 20°C, then 4 hrs at -10°C, then 12 hrs at 25°C, then 6 hrs at 45°C, then 14 hrs at 25°C.