



**Biologicals:
cold chain and temperature control
from product design to finished product**

Symposium Biologicals, Bonn, Oct. 2008

Symposium der Fachgruppe Arzneimittelkontrolle/Pharmazeutische Analytik in der DPhG

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The Product

Product Specific Cold Chain

Application of Cold Chain



The Product

- Identification of Product
- Identification of Container / closure
- Stability profile
- Other relevant aspects of finished product, e.g.
 - Additional components
 - End-user
 - Distribution channel



Temperature-Sensitive Products

- Proteins**
- Water**
- Labile chemical structures
- and others



Temperature Requirements

- ❖ Freezing needed / to be avoided

- ❖ Cooling needed

- ❖ Ambient temperature allowed

- ❖ Cold / warm cycles to be avoided



Temperature Control during handling

- ✓ Manufacturing operations
- ✓ Storage
- ✓ Transport



Biological Product Formulations

- Mannitol
- Sucrose
- Complexing agents
- Surfactants
- Other stabilisers (may be additional proteins)



Biological Product Presentations

- Glass vial
- Pre-filled syringe
- Freeze-dried
- Liquid formulation



Development Data

- ✓ Recovery during process steps
- ✓ Storage stability of intermediates
- ✓ **Stability studies** – accelerated // real time-temperature



Development Data

To be considered:

- ✓ Operations after start of shelf life (e.g.secondary packaging)
- ✓ Transport operations
- ✓ Storage locations during shelf life
 - Pharmaceutical warehouse
 - Pharmacy
 - Patient
 - “low tech environment” ► vaccines



Product Specific Cold Chain

- Define temperature requirements
- Define secondary / tertiary packaging
- Define routing and transport packaging
- Define testing documentation and testing requirements
- Execution of testing



Product Specific Cold Chain

- ❖ Define temperature requirements
 - Shelf life and storage temperature during shelf life
 - Time allowed for operations to be performed outside of storage temperature, if applicable
 - Time and temperature range for transport, if different from shelf life storage
 - Concept for dealing with deviations during transport / storage



Product Specific Cold Chain

- ❖ Define secondary / tertiary packaging
 - Materials used
 - Additional items added
 - One or more cartons in a unit pack
 - Type of tertiary packaging (carton, insulating container,...)



Product Specific Cold Chain

- ❖ Define routing and transport packaging
 - Truck, Ship, Airplane
 - Hubs
 - Service providers
 - Shipping container
 - Active cooling
 - Passive cooling



Product Specific Cold Chain

- ❖ Define testing documentation and testing requirements
 - Requirement Specification
 - Component Specification
 - Temperature records and recording locations
 - Routing records
 - Routing alternatives: by distance; by amount



Product Specific Cold Chain

- ❖ Execution of testing
 - Summer vs. Winter
 - Number and types of shipments
 - Qualification of Components vs. Qualification of Complete Shipping cycle



Application of Cold Chain

- Quality Systems and Training
- Evaluation of data
- Confirmation of definitions
- Temperature Control Strategy



Quality Systems and Training

The quality systems should include the following, as applicable:

- Approved written procedures and specifications
- Calibration program
- Stability program
- Qualification program
- Audit program
- Training



Quality Systems and Training

The quality systems should include the following, as applicable:

- Deviation and investigation program
- Corrective and preventive action (CAPA) program
- Periodic temperature-controlled process assessment
- Change control program
- Management controls



Quality Systems and Training

Training program

- Internal Training
- External Training
- Timing of Training
- Documentation of Training



Confirmation of definitions

- ❖ Cold Chain Components
 - Packaging
 - Routing

- ❖ Cold Chain Execution
 - Maximum Time of Transport
 - Extremes of Environmental Conditions
 - Results of Pre-Defined Tests



Temperature Control Strategy

- ❖ Temperature Data
 - Routine
 - Deviations and other special cases
 - Periodic Checks of the System



Temperature Control Strategy

❖ Deviation and CAPA System / Change Control

- Voluntary changes only after appropriate evaluation and with adequate control

❖ Management Overview

- Periodic Review of Functioning of Cold Chain and ancillary Systems



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THANK YOU FOR YOUR ATTENTION

