ABBOTT LABORATORIES

GMP aspects of cold chain management for pharmaceutical products

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Cold chain management for pharmaceutical products

Content

- Introduction
- Process flow analysis
- Pratical approach to validation/qualification
  - **-80°C storage/ frozen shipment**
  - **2-8°C shipment**
  - **Temperature excursion handling/data requirements**
- Training/documentation

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- Biotech products often require deep frozen/refridgerated storage
- Quality of pharmaceutical products is of primary concern
- Chemical and physico-chemical stability depends on temperature
- cGMP regulations enforce the compliance with strict temperature control along the process/distribution chain

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- cGMP regulations require
  - Complete tracking of temperature storage conditions
  - Validated storage areas
  - Qualified shipment
  - Documentation
  - Procedures to handle temperature excursions

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Process Flow Diagram [1)]

Identify Product

Product stability profile

Transportation process flow consideration

Bulk & Intermediate **Finished goods** **Analytical samples**

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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Process Flow Diagram [1)]

Develop requirements documents
Component specification

Design testing

Develop OQ protocol **Develop PQ protocol**

OQ testing **PQ testing**

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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Process Flow Diagram [1)]

Implement the process

Distribution chain training **Develop training**

Quality systems

Auditing distribution chain **Regulatory perspective**

Perform monitoring

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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- Definition of validation
  Validation is documented testing that consistently produces a result meeting pre-determined specifications.

- Definition of qualification
  Qualification is documented testing that demonstrates with a high degree of assurance that a specific process will meet the pre-determined acceptance criteria.

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- Example of a cold chain
  - Drug substance manufacture East coast US
  - Shipment at –80°C to drug product manufacturing site EU
  - Shipment of semi finished product at 2-8°C to distribution center in EU
  - Shipment of semi finished product to packaging site in US at 2-8°C
  - Distribution of final product to customer at 2-8°C

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- Temperature tracking during processing
  - Each manufacturing step at RT is captured
  - Each manufacturing step has an acceptance limit
  - Sum of all manufacturing steps has to be within limit
  - Total processing time at RT is covered by analytical stability data of the product

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- Qualification[1)] of storage equipment (eg freezer)
  - Calibration of sensors (pre/post validation)
  - Temperature distribution (empty/loaded)
  - Critical alarm functions tested
  - Predefined acceptance criteria
  - Written and preapproved protocols

1) Qualification: proving and documenting that equipment or ancillary systems are properly installed, work correctly, and comply with specified requirements

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- Validation of a freezer
  - External sensors calibrated to +/- 2°C
  - Data recording:
    - Every 5 min
    - Continously over 3 days
    - 15 sensors distributed within (bottom/middle/top) freezer
  - Equilibration period 3 h
  - Acceptance criteria:
    - No single value +/- 20°C of target
    - Mean of data per h: +/- 5°C
  - Recalibration every year
  - Revalidation every 2 years

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- Shipment qualification –80°C (endurotherm E90)




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Shipment qualification –80°C (endurotherm E90)




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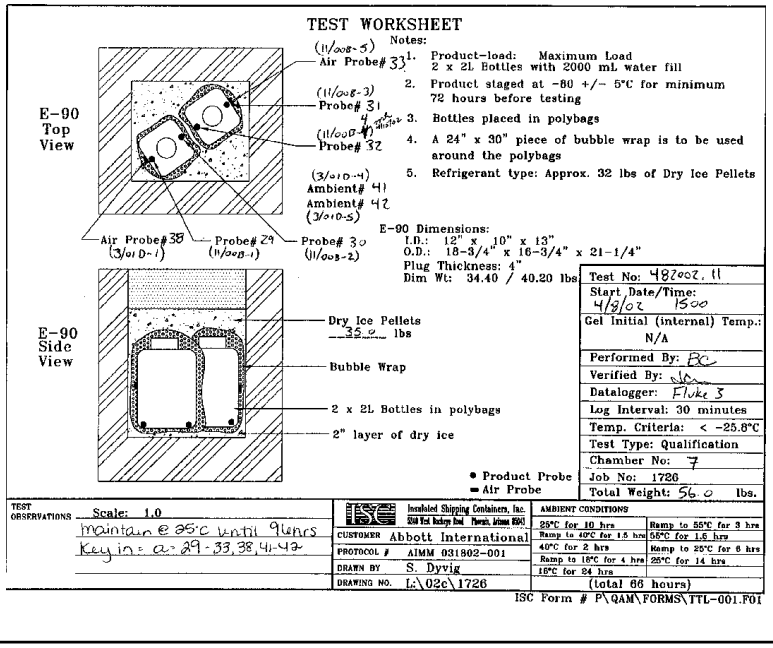
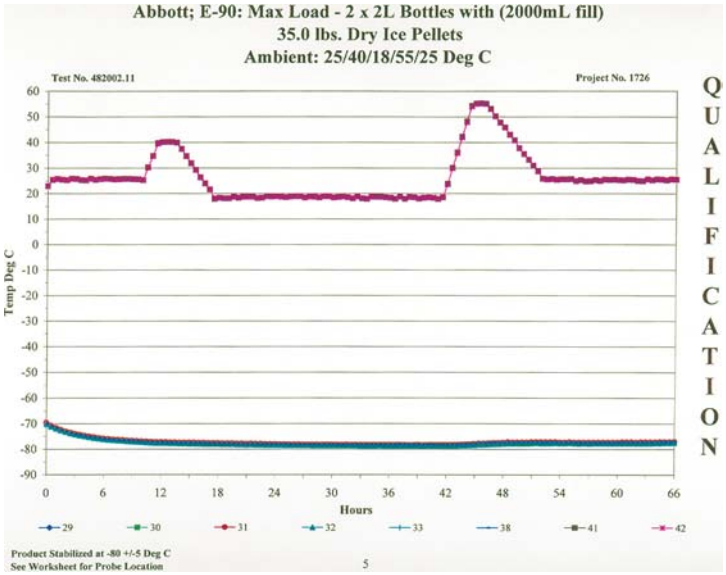
- Shipment qualification endurotherm E 90
  - Thermal qualification
    - Product temperature NMT –25°C for at least 66 h
    - Ambient temperature profile (+18°C to +55 °C)
    - 2 x 2L of product
    - Approx. 32 lbs dry ice refrigerant
  - Transportation qualification
    - Free fall testing (ASTM D 5276)
    - Vibration test (ASTM D 999)
    - Random vibration test (ASTM D 4228)





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- Shipment qualification EF 6100 [1)]
  - Thermal qualification
    - Product temperature 0 - 10°C for at least 72 h
    - 2 temperature profiles (-15°C to +18 °C and 25°C to 40°C)
    - 25600 units of product
    - Approx. 396 lbs refrigerant (48 oz ice brix, 5°C and –20°C)

1) manufactured by Tuscarora Thermosafe, formerly Insulated Shipping Container

EF-6100AB Packaging Diagram "Winter Profile"

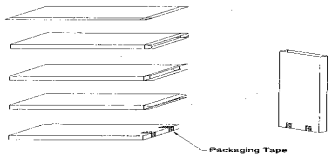


Figure 1: Gel Sleeve Assembly

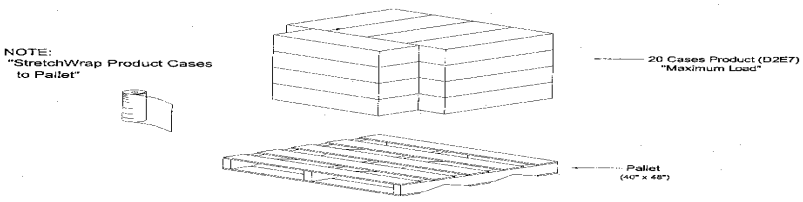


Figure 2: Product/Pallet Assembly

EF-6100AB Packaging Diagram "Winter Profile"

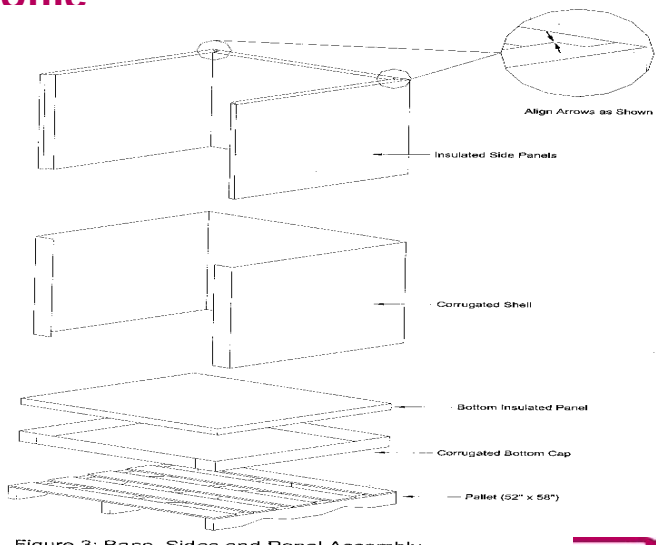


Figure 3: Base, Sides and Panel Assembly

EF-6100AB Packaging Diagram "Winter Profile"

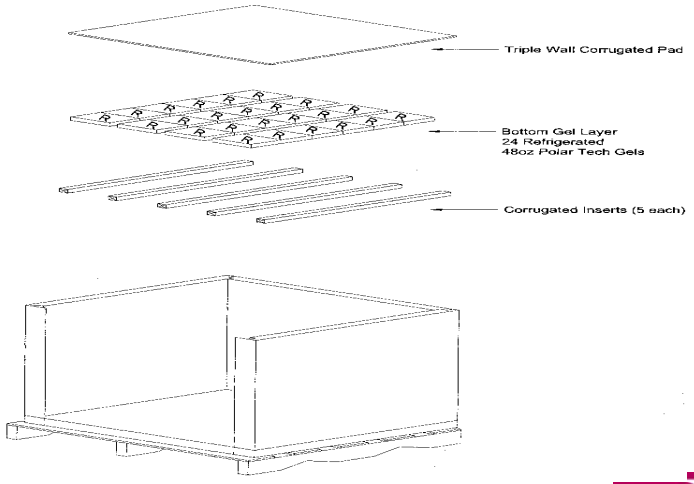


Figure 4: Bottom Gel layer, Spacer, and Pad Assembly

EF-6100AB Packaging Diagram "Winter Profile"

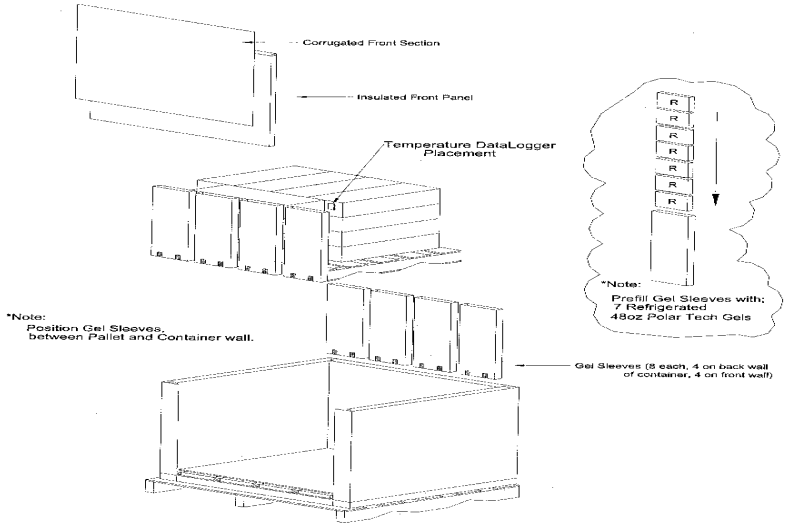


Figure 5: Gel Sleeve, Product Pallet, Front Wall Assembly

EF-6100AB Packaging Diagram "Winter Profile"

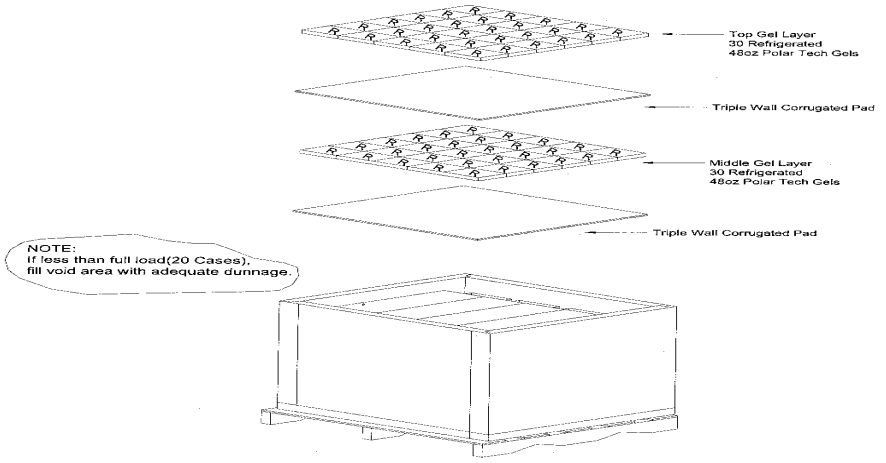


Figure 6: Top Gel Assembly

EF-6100AB Packaging Diagram "Winter Profile"

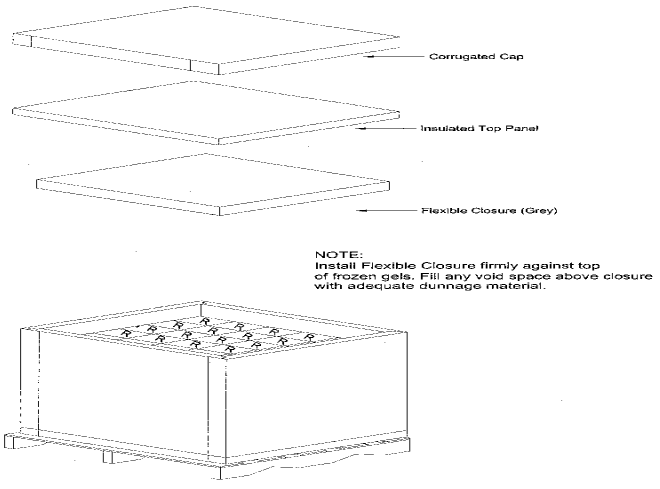


Figure 7: Top Container Assembly

EF-6100AB Packaging Diagram "Winter Profile"

NOTES FOR FINAL ASSEMBLY:
1. STRAP CONTAINER THREE (3) TIMES AROUND GIRTH
2. STRAP CONTAINER TO PALLET TWO (2) TIMES EACH DIRECTION
3. USE FIBERBOARD CORNER PROTECTORS ON ALL STRAPPED CORNERS

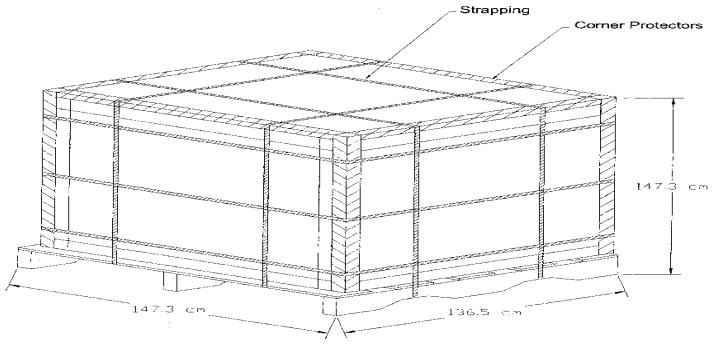
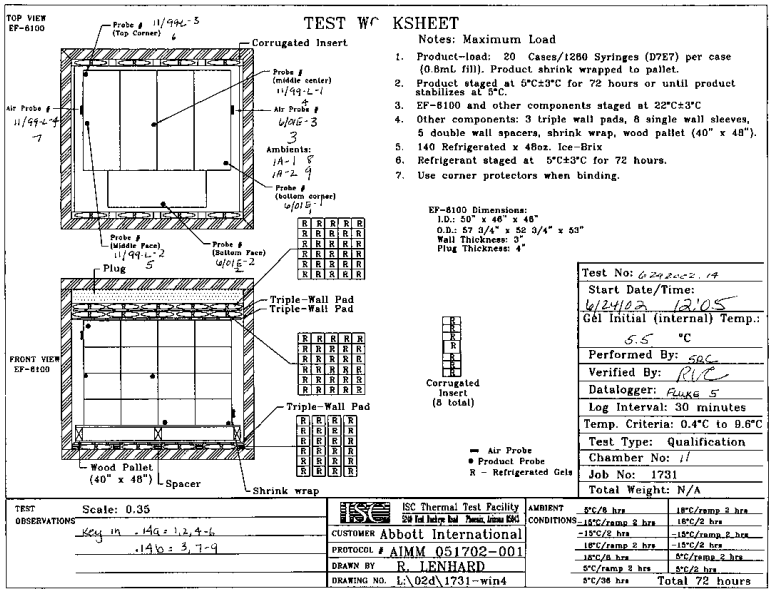
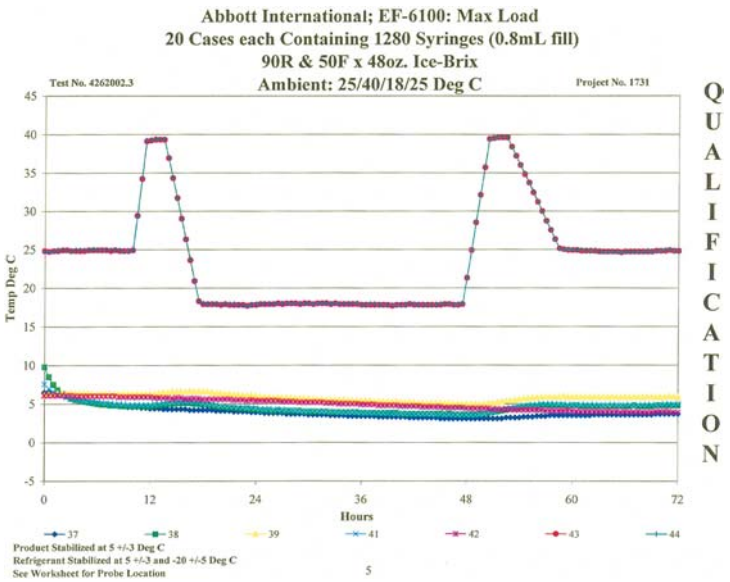
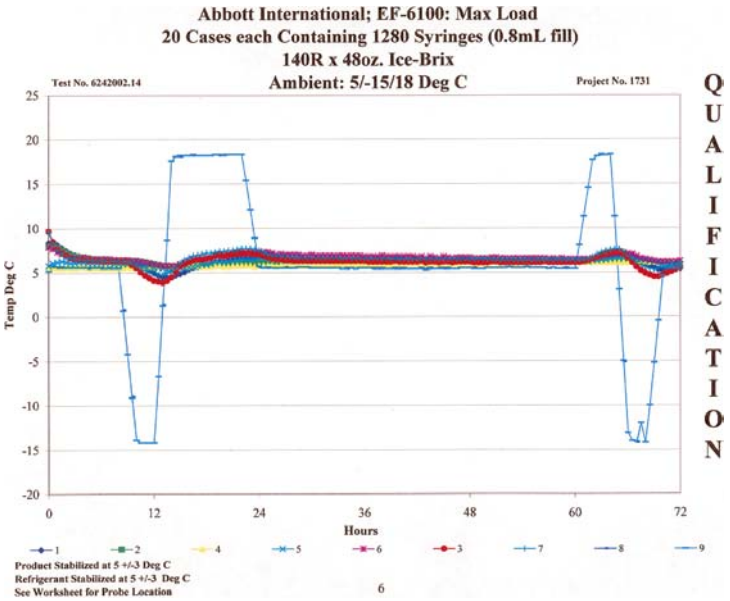


Figure 8: Strapping Assembly





QUALIFICATION



QUALIFICATION

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Example of a Temperature Excursion Study [1)]

Storage condition	Testing condition
Controlled room temperature 20-25°C	1) –20°C for 2 days 2) 60°C/75% RH for 2 days
Refridgerated condition 2-8°C	1) -20°C for 2 days 2) 40°C/75% RH for 2 days
Freezer condition -20 to –10°C	1) 25°C/60% RH for 2 days

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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Example of a Thermal Cycling Study [1)]

Storage condition	Testing condition
Controlled room temperature 20-25°C	–20°C for 2 days followed by 40°C/75% RH for 2 days Repeat for a total of 3 cycles
Refridgerated condition 2-8°C	-20°C for 2 days followed by 25°C/60% RH for 2 days Repeat for a total of 3 cycles
Freezer condition -20 to –10°C	-20°C for 2 days followed by 5°C for 2 days Repeat for a total of 3 cycles

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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Example for Temperature Excursion Handling of a refrigerated product[1)]

Temperature Range	Time
<-20°C	Do not use
-20°C to 2°C	2 days
2 to 8°C	Until Expiry
8 to 25°C	6 days
25 to 40°C	2 days
> 40°C	Do not use

1) According to a draft medicinal cold chain guideline by PDA Cold chain working group, Nov. 03

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- Training/documentation
  - According to written SOP's
  - Training must be documented
  - Specific with regards to
    - Preconditioning of refrigerants to be used
    - Packaging instructions
    - Handling of thermologgers
    - Paper work (preshipment notification, contact persons, deviation handling)
  - Temperature data for each shipment have to be evaluated against defined criteria

Acknowledgement

Kevin O'Donnell
Dr. M. Dickes
Joshua Froimson
ISC

End of Presentation