



GMP aspects of cold chain management for pharmaceutical products

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Cold chain management for pharmaceutical products

Content

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



Cold chain management for pharmaceutical products

- 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



Cold chain management for pharmaceutical products

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



Cold chain management for pharmaceutical products

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



Cold chain management for pharmaceutical products

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



Cold chain management for pharmaceutical products

Process Flow Diagram ¹⁾



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



Cold chain management for pharmaceutical products

- 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.



Cold chain management for pharmaceutical products

- 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 $2-8^{\circ}\text{C}$ to distribution center in EU
 - Shipment of semi finished product to packaging site in US at $2-8^{\circ}\text{C}$
 - Distribution of final product to customer at $2-8^{\circ}\text{C}$



Cold chain management for pharmaceutical products

- 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



Cold chain management for pharmaceutical products

- Qualification¹⁾ 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



Cold chain management for pharmaceutical products

- Validation of a freezer
 - External sensors calibrated to +/- 2°C
 - Data recording:
 - Every 5 min
 - Continuously 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



Cold chain management for pharmaceutical products

- Shipment qualification –80°C (endurotherm E90)



Cold chain management for pharmaceutical products

Shipment qualification –80°C (endurotherm E90)



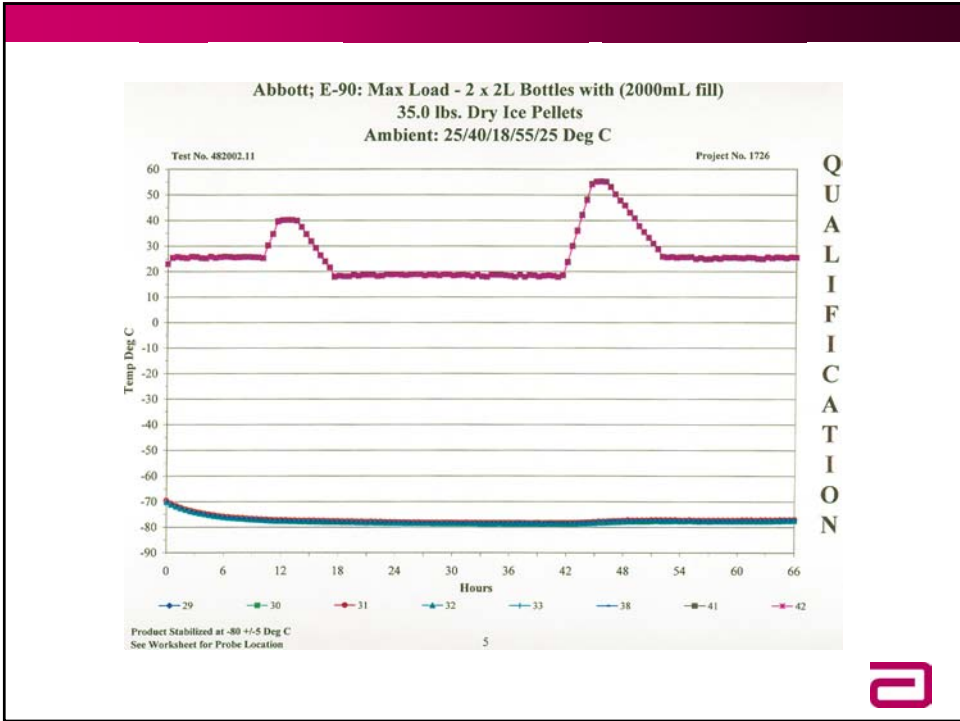
Cold chain management for pharmaceutical products

- Shipment qualification endurotherm E 90
 - Thermal qualification
 - Product temperature NMT -25°C for at least 66 h
 - Ambient temperature profile ($+18^{\circ}\text{C}$ to $+55^{\circ}\text{C}$)
 - 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)



TEST WORKSHEET													
<p>E-90 Top View</p>	<p>Notes:</p> <ol style="list-style-type: none"> 1. Product-load: Maximum Load 2 x 2L Bottles with 2000 ml. water fill 2. Product staged at $-80 \pm 5^{\circ}\text{C}$ for minimum 72 hours before testing 3. Bottles placed in polybags 4. A 24" x 30" piece of bubble wrap is to be used around the polybags 5. Refrigerant type: Approx. 32 lbs of Dry Ice Pellets 												
	<p>E-90 Dimensions:</p> <p>I.D.: 12" x 10" x 13" O.D.: 18-3/4" x 16-3/4" x 21-1/4" Plug Thickness: 4" Dim Wt: 34.40 / 40.20 lbs</p>												
<p>E-90 Side View</p>	<p>• Product Probe = Air Probe</p>												
<p>TEST OBSERVATIONS: Scale: 1.0 Maintain @ 25°C until 9 hrs Key in: a: 29, 33, 38, 41-42</p>	<table border="1"> <tr> <td> <p>Customer: Abbott International</p> <p>Protocol #: AIMM 031802-001</p> <p>Drawn By: S. Dyvig</p> <p>Drawing No.: L:\02e\1726</p> </td> <td> <p>AMBIENT CONDITIONS</p> <table border="1"> <tr> <td>25°C for 10 hrs</td> <td>Ramp to 55°C for 3 hrs</td> </tr> <tr> <td>Ramp to 40°C for 1.5 hrs</td> <td>55°C for 1.5 hrs</td> </tr> <tr> <td>40°C for 2 hrs</td> <td>Ramp to 25°C for 6 hrs</td> </tr> <tr> <td>Ramp to 15°C for 4 hrs</td> <td>25°C for 14 hrs</td> </tr> <tr> <td>15°C for 24 hrs</td> <td>(Total 66 hours)</td> </tr> </table> </td> </tr> </table>	<p>Customer: Abbott International</p> <p>Protocol #: AIMM 031802-001</p> <p>Drawn By: S. Dyvig</p> <p>Drawing No.: L:\02e\1726</p>	<p>AMBIENT CONDITIONS</p> <table border="1"> <tr> <td>25°C for 10 hrs</td> <td>Ramp to 55°C for 3 hrs</td> </tr> <tr> <td>Ramp to 40°C for 1.5 hrs</td> <td>55°C for 1.5 hrs</td> </tr> <tr> <td>40°C for 2 hrs</td> <td>Ramp to 25°C for 6 hrs</td> </tr> <tr> <td>Ramp to 15°C for 4 hrs</td> <td>25°C for 14 hrs</td> </tr> <tr> <td>15°C for 24 hrs</td> <td>(Total 66 hours)</td> </tr> </table>	25°C for 10 hrs	Ramp to 55°C for 3 hrs	Ramp to 40°C for 1.5 hrs	55°C for 1.5 hrs	40°C for 2 hrs	Ramp to 25°C for 6 hrs	Ramp to 15°C for 4 hrs	25°C for 14 hrs	15°C for 24 hrs	(Total 66 hours)
<p>Customer: Abbott International</p> <p>Protocol #: AIMM 031802-001</p> <p>Drawn By: S. Dyvig</p> <p>Drawing No.: L:\02e\1726</p>	<p>AMBIENT CONDITIONS</p> <table border="1"> <tr> <td>25°C for 10 hrs</td> <td>Ramp to 55°C for 3 hrs</td> </tr> <tr> <td>Ramp to 40°C for 1.5 hrs</td> <td>55°C for 1.5 hrs</td> </tr> <tr> <td>40°C for 2 hrs</td> <td>Ramp to 25°C for 6 hrs</td> </tr> <tr> <td>Ramp to 15°C for 4 hrs</td> <td>25°C for 14 hrs</td> </tr> <tr> <td>15°C for 24 hrs</td> <td>(Total 66 hours)</td> </tr> </table>	25°C for 10 hrs	Ramp to 55°C for 3 hrs	Ramp to 40°C for 1.5 hrs	55°C for 1.5 hrs	40°C for 2 hrs	Ramp to 25°C for 6 hrs	Ramp to 15°C for 4 hrs	25°C for 14 hrs	15°C for 24 hrs	(Total 66 hours)		
25°C for 10 hrs	Ramp to 55°C for 3 hrs												
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40°C for 2 hrs	Ramp to 25°C for 6 hrs												
Ramp to 15°C for 4 hrs	25°C for 14 hrs												
15°C for 24 hrs	(Total 66 hours)												
<p>Test No: 482002.11 Start Date/Time: 4/8/02 1500 Gel Initial (internal) Temp.: N/A Performed By: BC Verified By: [Signature] Datalogger: Fluke 5 Log Interval: 30 minutes Temp. Criteria: $< -25.8^{\circ}\text{C}$ Test Type: Qualification Chamber No: 7 Job No: 1726 Total Weight: 56.0 lbs.</p>	<p>ISC Form # P:\QAM\FORMS\TTL-001.F01</p>												





Cold chain management for pharmaceutical products

- 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"

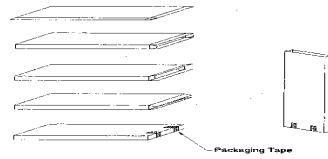


Figure 1: Gel Sleeve Assembly

NOTE:
"StretchWrap Product Cases
to Pallet"

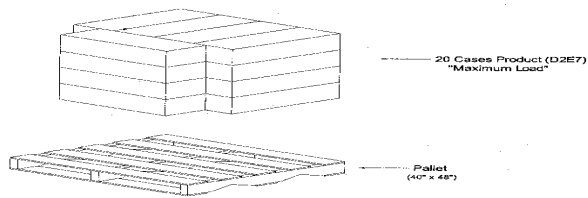


Figure 2: Product/Pallet Assembly



EF-6100AB Packaging Diagram "Winter Profile"

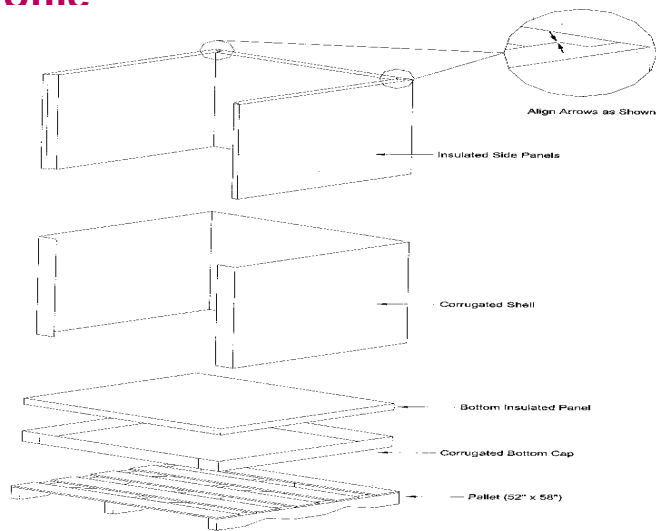


Figure 3: Base, Sides and Panel Assembly



EF-6100AB Packaging Diagram “Winter Profile”

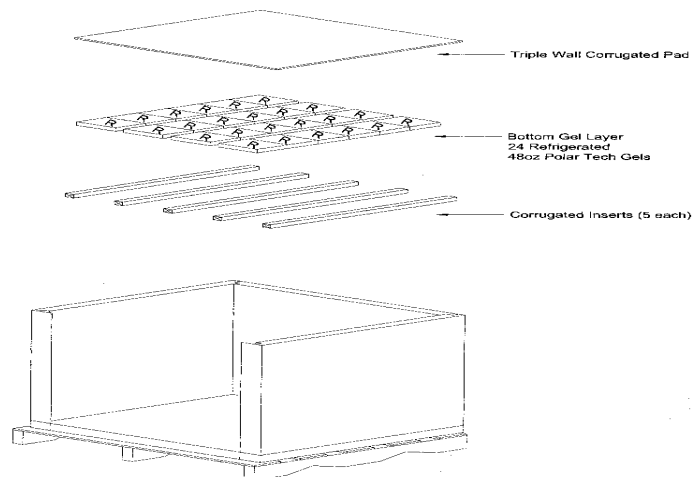


Figure 4: Bottom Gel layer, Spacer, and Pad Assembly



EF-6100AB Packaging Diagram “Winter Profile”

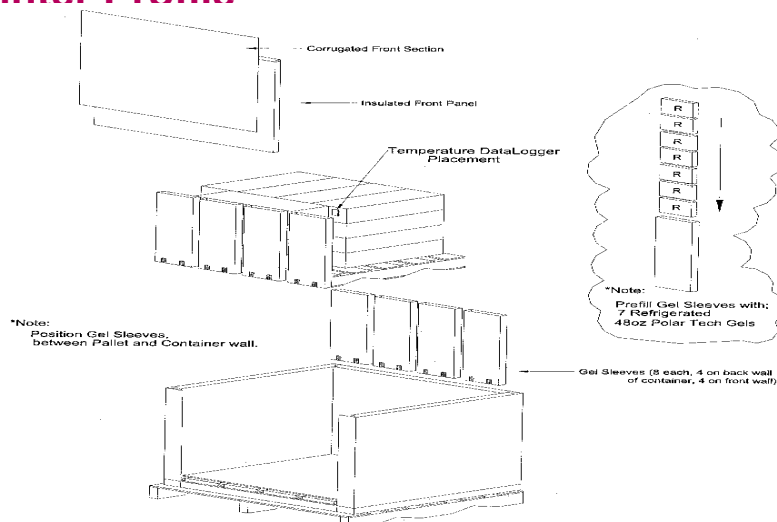


Figure 5: Gel Sleeve, Product Pallet, Front Wall Assembly



EF-6100AB Packaging Diagram “Winter Profile”

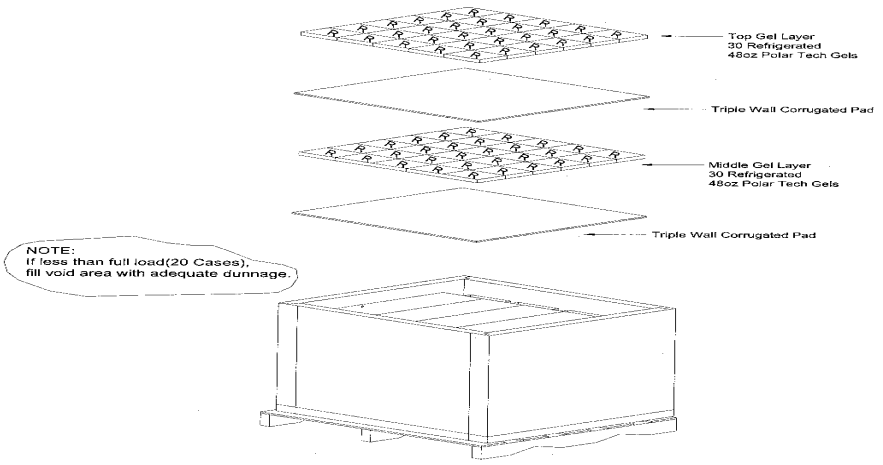


Figure 6: Top Gel Assembly



EF-6100AB Packaging Diagram “Winter Profile”

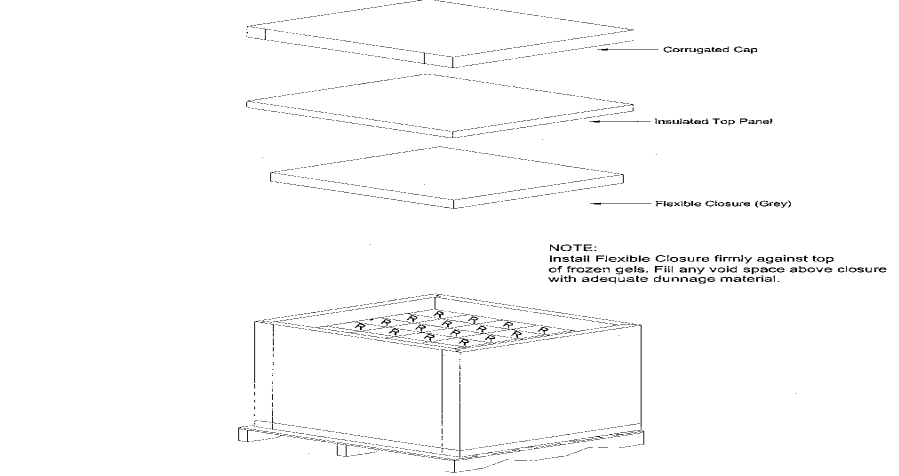


Figure 7: Top Container Assembly



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

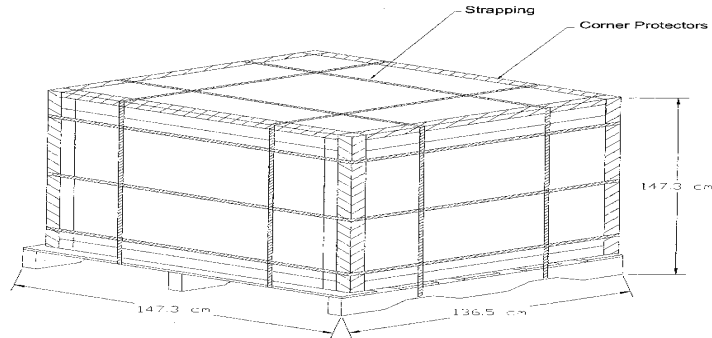


Figure 8: Strapping Assembly



TEST WORKSHEET

Notes: Maximum Load

- Product-load: 20 Cases/1200 Syringes (D727) per case (0.8mt fill). Product shrink wrapped to pallet.
- Product staged at 5°C±3°C for 72 hours or until product stabilizes at 5°C.
- EF-6100 and other components staged at 22°C±3°C
- Other components: 3 triple wall pads, 8 single wall sleeves, 5 double wall spacers, shrink wrap, wood pallet (40" x 48").
- 140 Refrigerated x 48oz. Ice-Brix
- Refrigerant staged at 5°C±3°C for 72 hours.
- Use corner protectors when binding.

EF-6100 Dimensions:
 I.D.: 50" x 48" x 48"
 O.D.: 57 3/4" x 52 3/4" x 55"
 Wall Thickness: 3"
 Plug Thickness: 4"

TEST OBSERVATIONS

Scale: 0.35

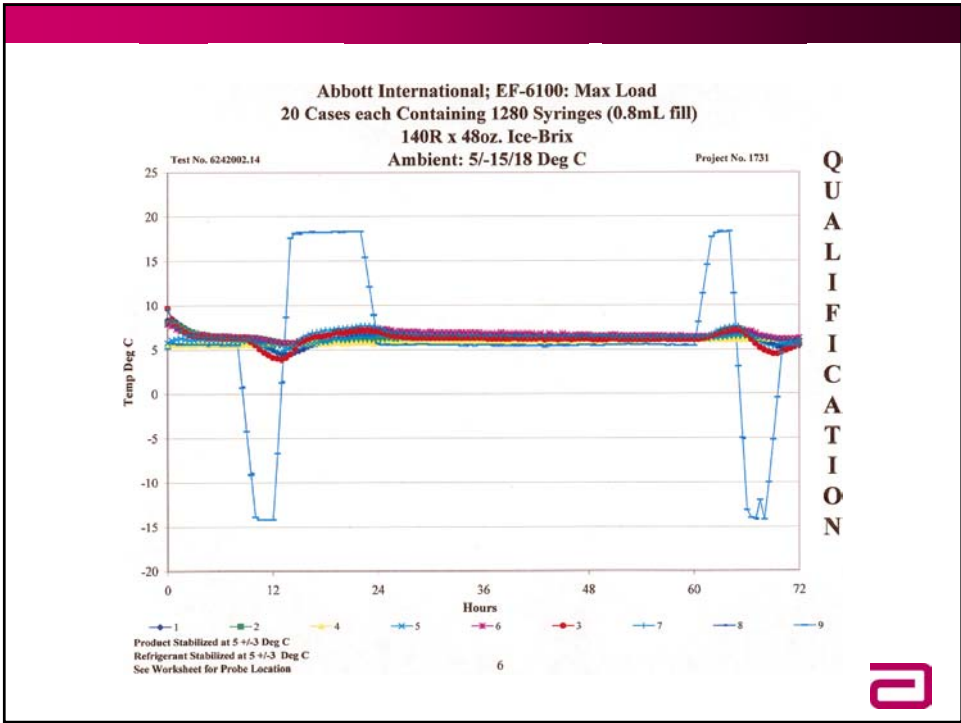
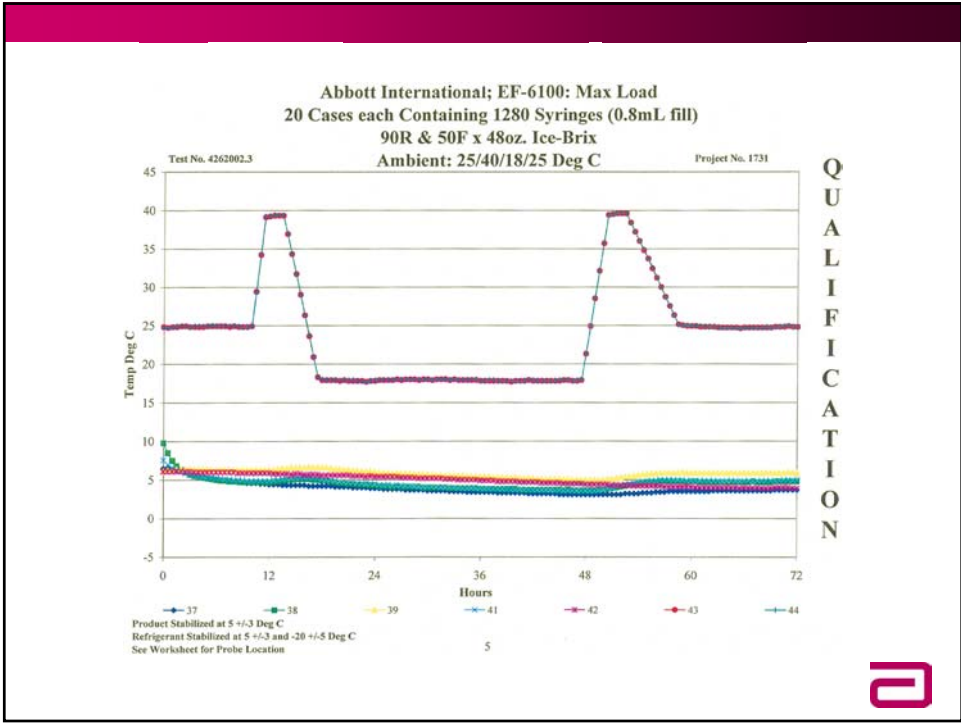
14a = 1, 2, 4-6
 14b = 3, 7-9

ISC Thermal Test Facility
 SP Test Entry Tool Form, Issue 002
 CUSTOMER: Abbott International
 PROTOCOL: AIMM 051702-001
 DRAWN BY: R. JENBARD
 DRAWING NO. L:\02d\1731-win4

AMBIENT: 5°C/8 hrs
 CONDITIONS: 18°C/ramp 2 hrs
 -15°C/2 hrs
 18°C/ramp 2 hrs
 18°C/ramp 2 hrs
 5°C/ramp 2 hrs
 5°C/36 hrs
 18°C/ramp 2 hrs
 -15°C/ramp 2 hrs
 18°C/ramp 2 hrs
 5°C/ramp 2 hrs
 5°C/36 hrs
 Total 72 hours

TEST No: 0242002 14
 Start Date/Time: 12/24/02 12:05
 Gel Initial (internal) Temp.: 5.5 °C
 Performed By: SBC
 Verified By: RUC
 Datalogger: Flux 5
 Log Interval: 30 minutes
 Temp. Criteria: 0.4°C to 9.6°C
 Test Type: Qualification
 Chamber No: 11
 Job No: 1731
 Total Weight: N/A





Cold chain management for pharmaceutical products

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
Refrigerated 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



Cold chain management for pharmaceutical products

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
Refrigerated 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



Cold chain management for pharmaceutical products

Example for Temperature Excursion Handling of a refrigerated product¹⁾

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



Cold chain management for pharmaceutical products

- 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



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End of Presentation

