

The story behind the story !  
What the PDA Technical Report 39 is all  
about.

Sar Mishra

Supply Partnership Site

Wyeth

April 11' 2007 NEPDA Meeting

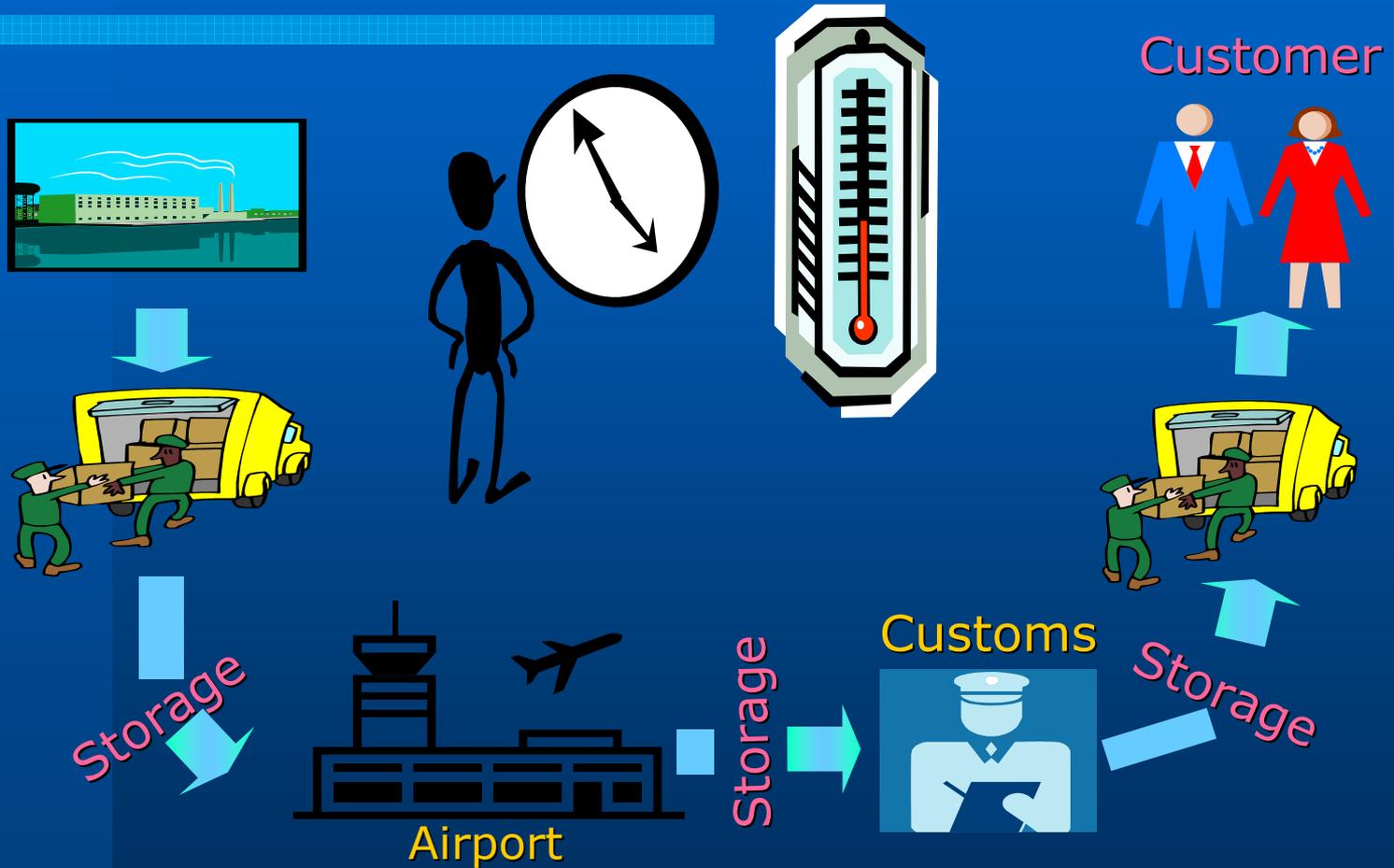
# Presentation Overview

- **Cold Chain Overview**
- **Why was a cold chain guidance needed ?**
- **Key concepts in the TR 39 guidance**
- **The TR 39 development process**
- **Cold Chain related regulatory observations**
- **Detailed discussion of TR 39**
- **Continuous Monitoring & Improvement**
- **Conclusion**

# Cold Chain Overview

- **What is cold chain ?**
- **Why do companies need cold chain management ?**
- **What are the regulatory expectations regarding cold chain and company responsibility ?**

# The Transportation Environment “In-Transit”



# What is Cold Chain ?

- **The sequence of transportation events from the manufacture of the Formulated Bulk material, through the Final Packaged product in the end user's possession that maintain temperature sensitive products within approved temperature specifications.**
- **Maintaining temperature control during these transportation events ensures that product quality, safety, efficacy and stability are maintained.**

# Why do companies need to manage their cold chain ?

- **Product name = company name in transit**
  - reputation, responsibility, liability.
- **Maintain product quality until patient use**
  - “end of chain”, customer compliance.
- **Increase compliance**
  - Reduce in-transit product deviations, complaints, recalls & tampering.
- **Reduced inventory pressures.**
- **Reduce cycle time pressures.**
- **All adds up ! –manage TIME & MONEY.**

# What is the regulatory expectation regarding cold chain?

- **Biopharm product growth explodes.**
- **Stability:**
  - to support excursions.
- **Qualification:**
  - seasonal shipping configuration
  - load size
- **Monitoring:**
  - shipping temperatures to ensure quality.
- **Partnering:**
  - with suppliers (components & distribution)
- **Complement FDA's General Principles of Process Validation (CDER, 1987, rev 2004)**

# Why was a cold chain guidance needed ?

- No FDA guidance for cold chain existed
- Lack of standards in industry.
- Provide current and new companies with essential principles and practices for temperature sensitive product transport.
- Attempt to harmonize cold chain practices across industry, geography, agency.
- Provide a qualification and cold chain management approach and process.



RISK

# Cold Chain guidance needed...

- **Regulatory scrutiny on company cold chain has increased worldwide.**
- **Temp sensitive products represent unique shipping challenges versus chemical drugs.**
- **Inconsistent expectations seen among regulatory authorities and officials in the same authority.**

# Other Guidance for Cold Chain

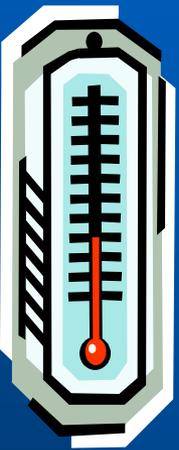
- EU- Good Distribution Practice of Medicinal Products (1994).
- WHO- Good Distribution Practice for Pharmaceutical Products (2004 draft).
- Canada- Temperature Control of drug products during Storage and Transportation (2004 draft).
- ISTA 7D- Thermal Controlled transport packaging for Parcel delivery shipment.
- USP <1079>- Good Distribution Practices.
- USP <1118>- Monitoring devices (t, T, RH).

# Key concepts in TR 39 guidance for cold chain

- **TR 39 Title**
- **TR 39 Concepts**

# TR 39 Title

- TR 39, September/October 2005, Supplement, Volume 59, No.S-3:  
**“Cold chain guidance for medicinal products: Maintaining The Quality Of Temperature-Sensitive Medicinal Products Through The Transportation Environment.”**



Customs



# TR 39 Concepts (in scope)

- **Cold Chain**

- Shipping, in-transit
- Manufacturer to end user
- Warehouse(Shipping) → Receiving Site
- Uncontrolled points in transit
- Chain of custody – outside of the company

- **Medicinal Products**

- Pharmaceuticals (Injectables, Oral, etc..)
- Vaccines
- Diagnostics
- Animal Products

# TR 39 Concepts (in scope)...

## ● Product Type...

- Finished products (Unlabelled bulk drug, labeled drug, finished packaged in kits)
- Active Pharmaceutical Ingredients (Bulk drug substance, etc)
- Process Intermediates (ie, Column eluates)
- Samples (GMP testing)
- Reference Standards

# TR 39 concepts...

- **Maintaining Quality of Product during shipping:**
  - To Certificate of Analysis requirements.
  - To Specifications in release testing OR shipping OR stability.
  - To Temperature/time limits allowed from excursion studies.
- **Temperature Sensitive Product**
  - **Specialized package to protect product.**
  - Controlled storage (as much as possible).
  - Minimize time out of refrigeration (TOR).
- **Transportation Environment**
  - Agents, Forwarders,
  - Customs, Inspections

# The Process: How was TR 39 developed ?

- Who are the PCCDG ?
- PDA's involvement
- Timeline for TR 39 development
- What's next ?

# The Process: Who are the PCCDG?

- 2002- Few members attempted to gather cold chain practices by current industry.
- **Pharmaceutical Cold Chain Discussion Group**
  - part of PDA.
- 2003
  - 12 members met at Bethesda (PDA).
  - PDA did not grant us Interest Group status
  - PCCDG pledged to commit to completing guidance.
- 2004
  - Membership expanded to 20 Pharma companies.
- 2005
  - Membership to 50 Pharma & Suppliers (145 + reps).

# Some faces of the PCCDG- TR39 development meeting @ Amgen

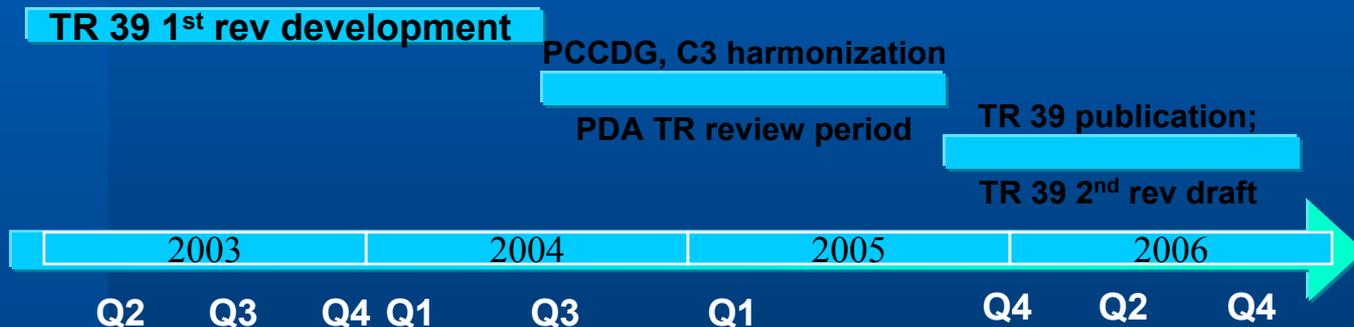


# The Process: PDA's involvement

- **Why PCCDG decided to work with PDA:**
  - A respected professional organization.
  - Pool of talented, experienced members
  - Good track record for publishing.
  - Facilities at disposal of members.
  - Scientific Advisory Board support.
  - Broad, international audience existed.

# The Process: TR 39 Timeline

- PCCDG



# TR 39 Timeline- 2003

- Q1, 2003 (PDA)
  - Guidance concept discussed and PFD developed.
- Q2, 2003 (Genentech)
  - Guidance written.
- Q3, 2003 (Amgen)
  - TR publication & presentation at PDA discussed.
- Q4, 2003
  - PDA Annual Meeting, Atlanta presentation.
  - Draft TR sent to PDA/website.

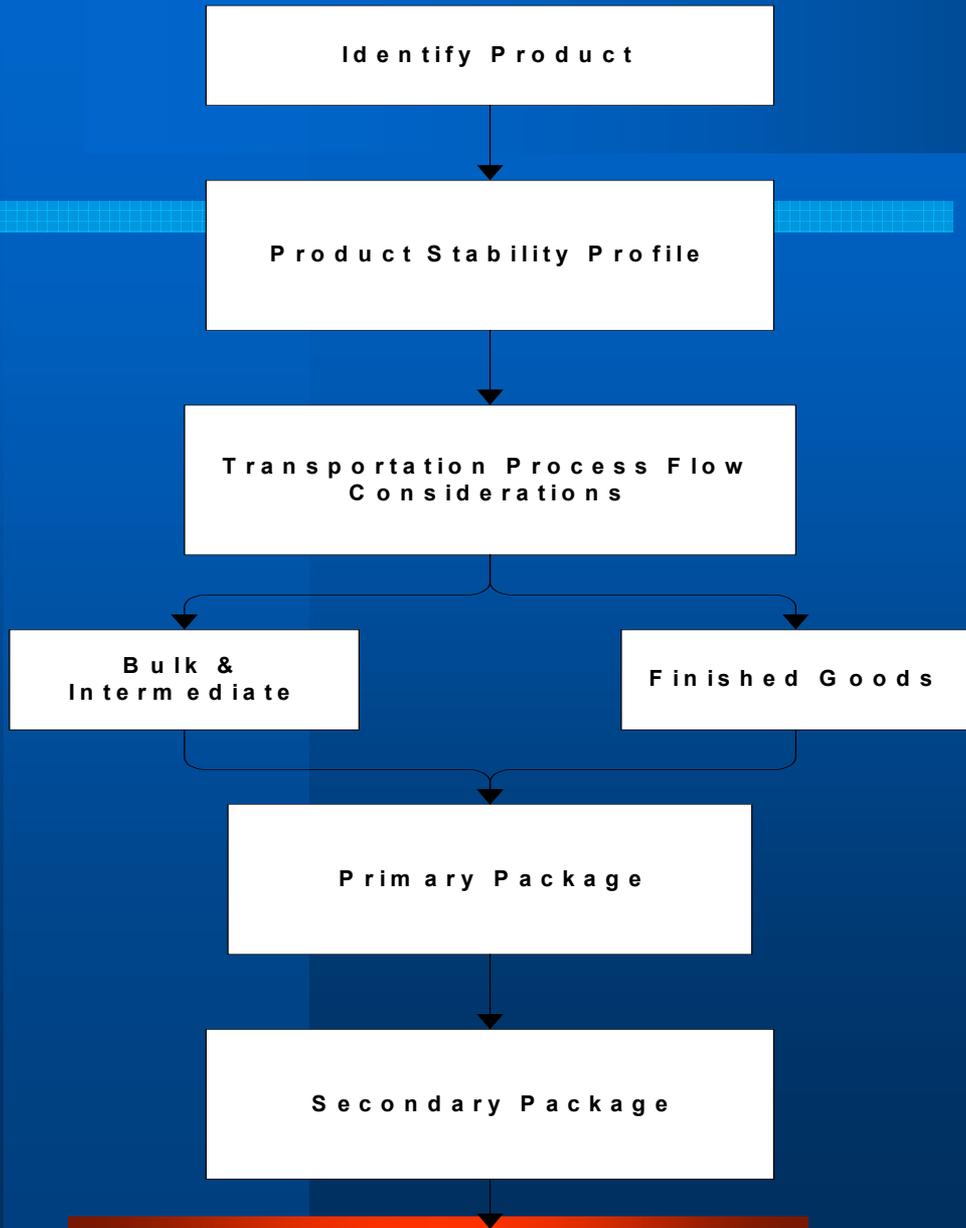
# TR 39 Timeline- 2004

- **Q1, 2004**
  - Received comments from PDA web.
  - PCCDG presented TR draft at PDA International conference- Basel, SZ.
- **Q2, 2004 (Wyeth)**
  - TR draft discussed.
- **Q3, 2004 (Lilly)**
  - TR Draft finalized;
  - Sent to PDA SAB for comment.
- **Q4, 2004 (Abbott)**
  - TR Final revisions made.
- **Q1, 2005**
  - TR Approval by PDA SAB.
- **Q3, 2005: TR published by PDA:Vol 59, S3**

# The Process: What's next ?

- An expanded cold chain group formed with international focus.
- C3 (EU) = Cold Chain Committee
- PLF = Pharma Logistics Forum
- PCCDG + C3 + PLF = TPG (Temperature-controlled Pharmaceuticals Group).
- TPG will solicit regulatory and pharmacopoeia input from various countries.
- TPG will attempt to harmonize cold chain requirements and practices across industry.
- TR 39 second revision is developed in draft stage.

# Detailed discussion TR39: Identification



Identification of Process

# Product Stability Studies

- **Design:**

- **These studies will expose drug product to temperature conditions both within and outside storage conditions**
- **Long term stability study – ICH Q1A**
- **Accelerated stability study – ICH Q1A**
- **Temperature excursion study – PCCDG Proposal**
- **Thermal cycling study – FDA Draft Guidance/PCCDG Proposal**

# Identification : Example of a type of Stability Study

## Temperature Excursion Study

Long Term Storage Condition	Testing at Extreme Conditions ICH Q1A	Testing Condition WHO Annex 5
Controlled Room Temperature 20 to 25 °C	1) -20 °C for 2 days 2) 60 °C/75% RH for 2 days	-----
Refrigerated Condition 2 to 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	-----

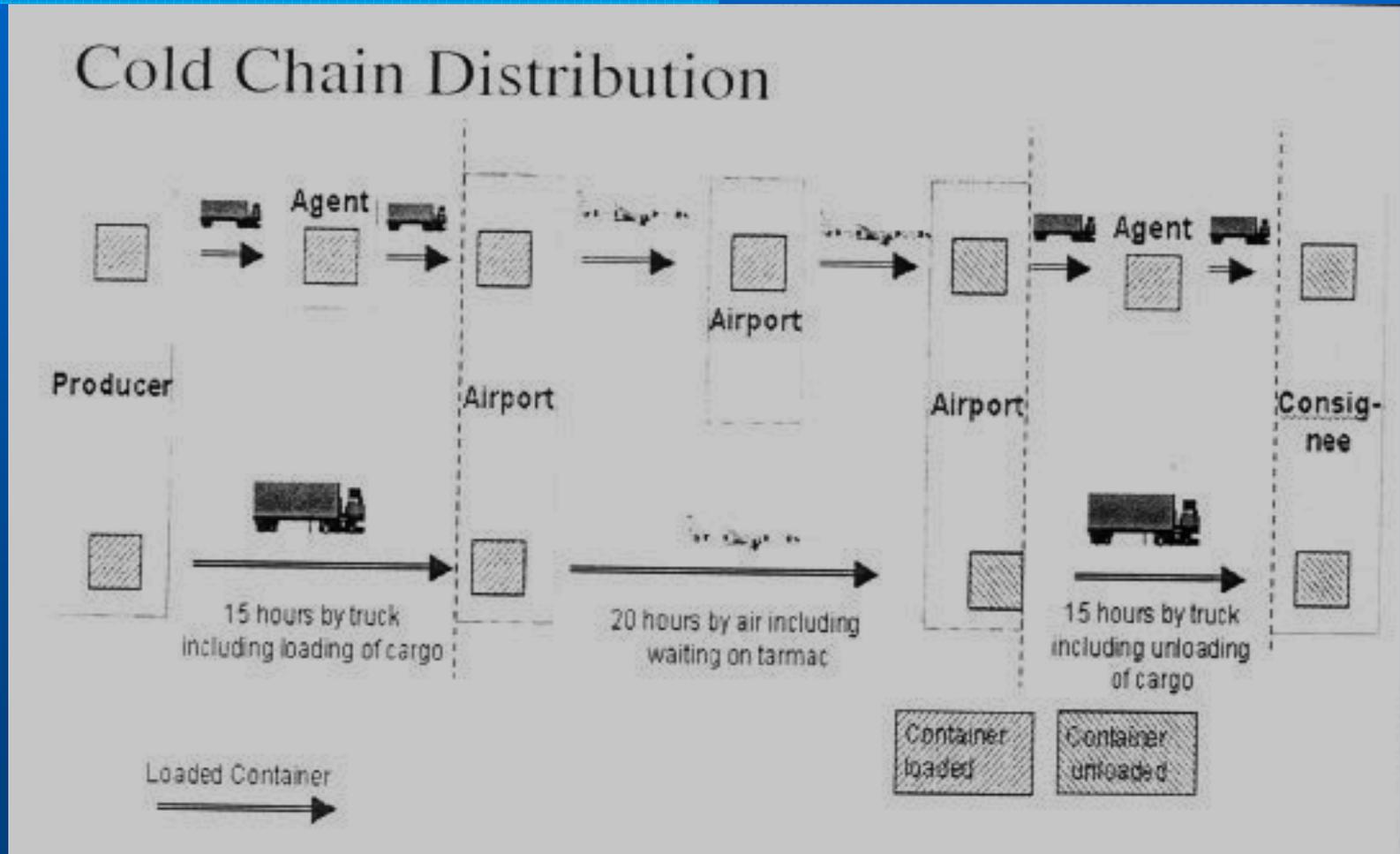
# Identification : Product Specification

Product-Specific Stability Data to Determine the effect of Temperature Excursions

Storage Condition: Refrigerated Condition (2 to 8 °C)

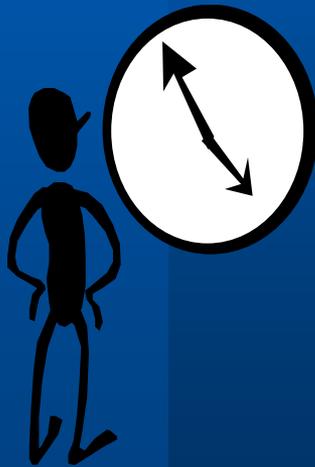
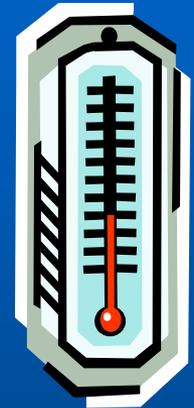
Temperature Exposure Range	Max use time for product
<-20 °C (<-4 °F)	Do Not Use
-20 to 2 °C (-4 to 36 °F)	2 days
2 to 8 °C (36 to 46°F)	Until Expiry
8 to 25 °C (46 to 77 °F)	6 days
25 to 40 °C (77 to 104 °F)	2 days
>40 °C (104 °F)	Do Not Use

# Cold Chain for a typical company



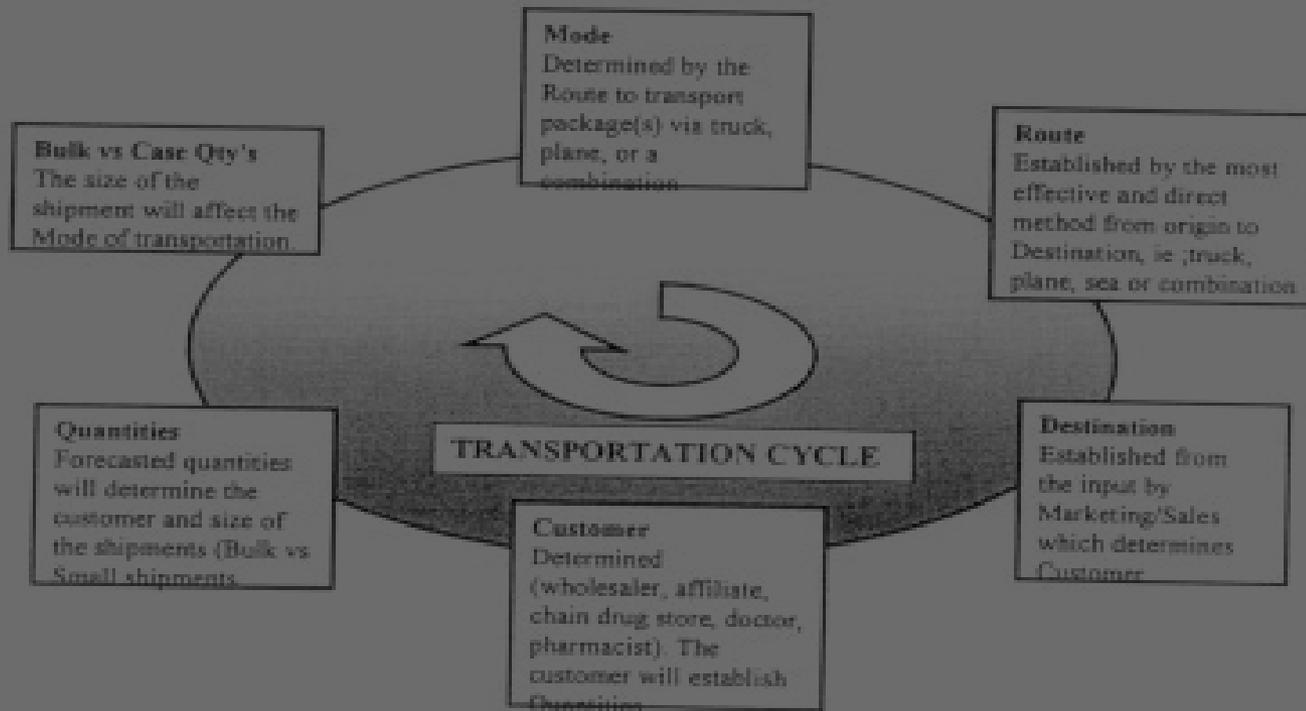
# Transport Process Involves:

Ambient Temperature Variance  
Modes of Transportation  
Transit Duration  
Route  
Material Handling



# Identification : What factors determine the mode of transportation (ie, truck/air)?

## Mode Determination



# Distribution Environment

- **Medicinal products are transported in a commercial environment (as opposed to a controlled lab).**
- **The following factors impact actual conditions a specific shipment may encounter:**
  - Unforeseen transport events
  - Weather !
- **Consider these factors, when:**
  - Designing test protocols
  - Understanding 'anticipated extremes'

# Identification: Packaging- Primary and Secondary

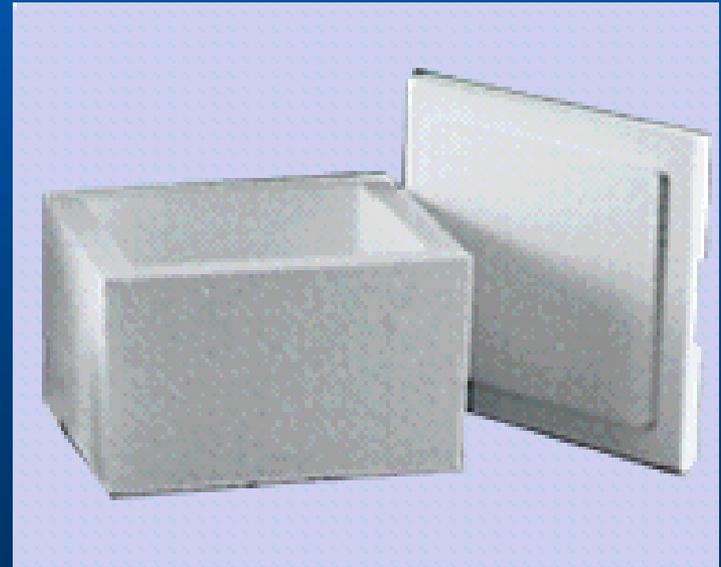
**Dense Pack – easier to  
control temperature**

**Air Pack – more  
difficult to control  
temperature**



# Identification: Packaging-Tertiary or Shipping/Distribution

- **Definition: Packaging used solely for shipping/distribution.**
- **Example: Corrugated carton; insulated shipper for temperature-sensitive products; dunnage; refrigerants.**



# Detailed discussion of TR 39: Development of Process



# Development: Requirements Document are

- **Summary of the Identification Process**
- **Inputs for Design Qualification test.**
- **Functional Specifications for:**
  - 1.) Stability requirements.**
  - 2.) Packaging requirements.**
  - 3.) Transport requirements.**

# Development: Packaging Specs needed:

- To determine appropriate packing configurations
- To determine the minimum and maximum loads
- To determine product proximity to gel packs, container wall, temperature monitors (DESIGN)

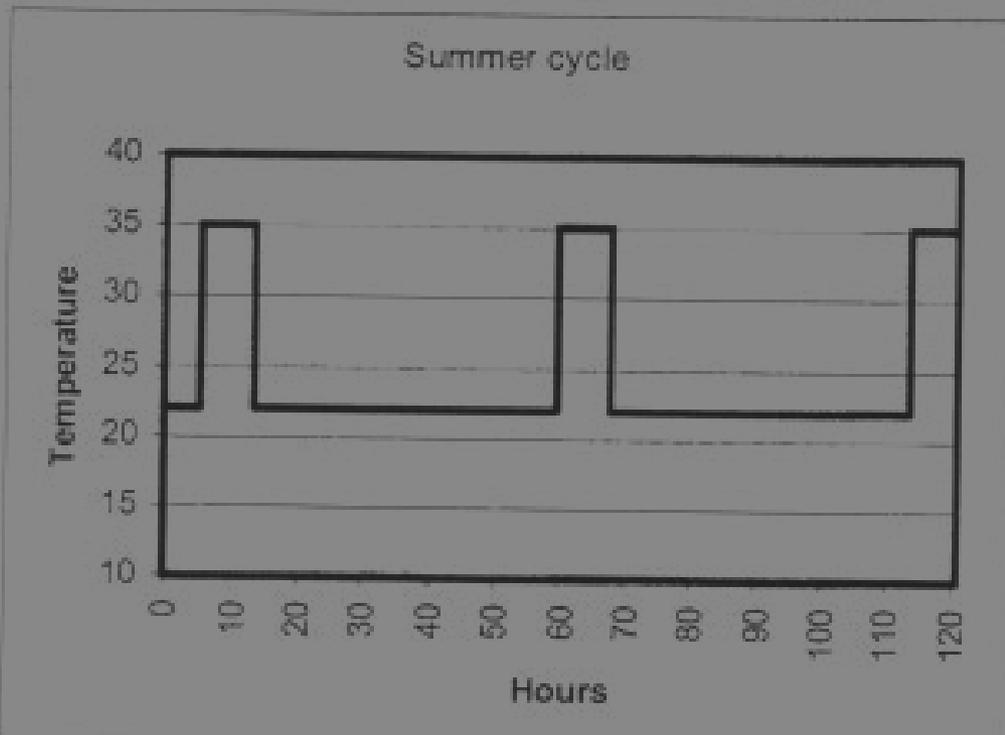


# Development: Example of Components Specs

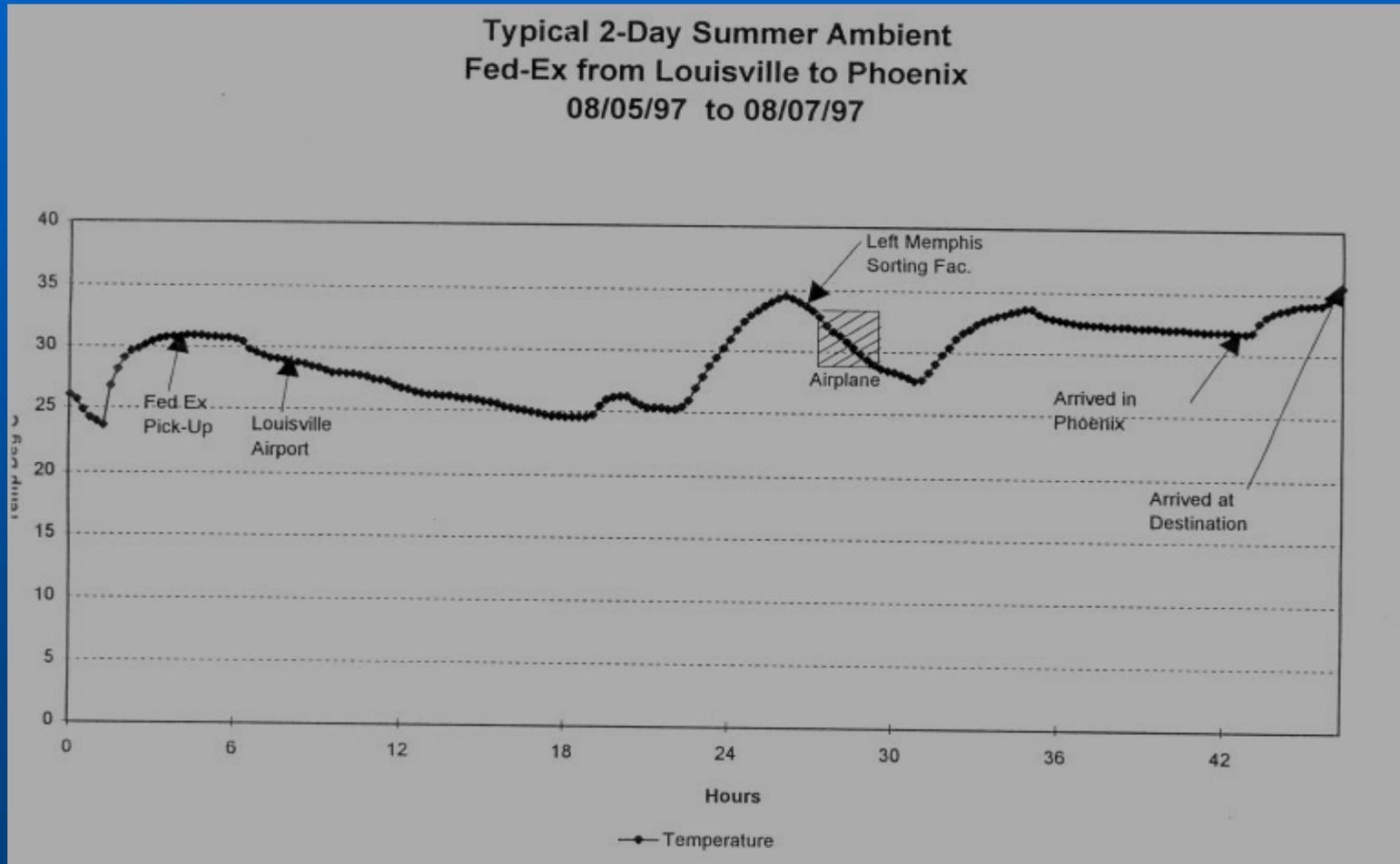
- **Insulated Shippers**
  - weight, size, thickness, conductivity 'R' value.
- **Coolant**
  - gel pack, weight, size, material and characteristics.
- **Temperature monitors**
  - calibration, fragility, temperature limits.

# Development: Time/Temp Profiles

## Development and use of Shipping temperature test cycles



# Development: Time/Temp Live Shipment



# Development: Live shipment weekly data

Week by Week Summary  
Louisville to Phoenix

Week	Maximum Temperature Recorded in Deg C	Minimum Temperature Recorded in Deg C	Average Temperature in Deg C	Number of Spikes Above 30 Deg C	Average Spike Time Above 30 Deg C in Hours	Average Spike Temperature Above 30 Deg C	Total Number of Trips	Average Trip Length
1	44.1	14.8	23.8	4	6.1	38.8	4	58.1
2	49.7	13.6	24.4	1	0.5	30.3	1	63.5
3	37.1	14.9	25.0	3	14.5	32.2	3	46.1
4	45.6	13.5	27.1	10	6.3	32.4	3	55.2
5	48.7	19.4	32.9	5	25.7	35.9	2	90.4
6	45.3	14.4	26.8	6	6.2	33.0	3	55.8
7	52.0	15.8	31.2	5	16.5	36.2	3	46.3
8	53.4	16.4	29.1	28	2.8	35.4	3	58.2
9	45.2	21.7	29.2	5	9.8	32.6	2	77.9
10	38.7	21.9	27.3	8	11.5	32.5	3	81.7
11	N/A	N/A	N/A	N/A	N/A	N/A	0	N/A
12	41.5	21.2	28.5	6	8.5	33.4	4	45.4
13	37.4	22.4	30.0	5	4.1	32.6	1	49.8
14	46.8	11.8	27.4	5	9.0	33.8	2	55.8
15	46.9	11.2	23.5	3	5.7	34.8	2	55.0

Week 1 = June 1 to June 7  
 Week 2 = June 8 to June 14  
 Week 3 = June 15 to June 21  
 Week 4 = June 22 to June 28  
 Week 5 = June 29 to July 5

Week 6 = July 6 to July 12  
 Week 7 = July 12 to July 19  
 Week 8 = July 20 to July 26  
 Week 9 = July 27 to August 2  
 Week 10 = August 3 to August 9

Week 11 = August 10 to August 16  
 Week 12 = August 17 to August 23  
 Week 13 = August 24 to August 30  
 Week 14 = August 31 to September 6  
 Week 15 = September 7 to September 13

Table 2.

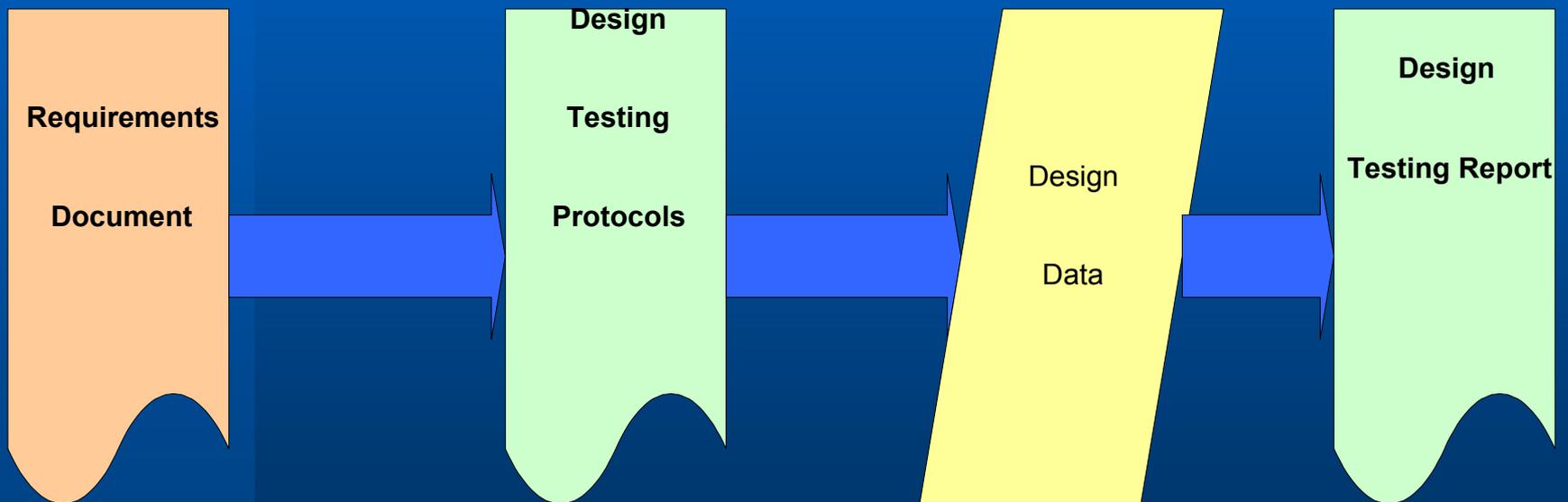
# Development: Live shipment monthly data

Month by Month Summary  
Louisville to Phoenix

Month	Maximum Temperature Recorded in Deg C	Minimum Temperature Recorded in Deg C	Average Temperature in Deg C	Number of Spikes Above 30 Deg C	Average Spike Time Above 30 Deg C In Hours	Average Spike Temperature Above 30 Deg C	Total Number of Trips	Average Trip Length
June	49.7	13.5	25.1	18	7.3	33.1	11	58.6
July	53.4	14.4	32.9	49	7.6	35.2	13	58.5
August	41.5	21.2	28.5	19	8.2	32.8	8	59.5
September	46.9	11.2	25.5	8	17.5	34.1	4	55.4

Table 4.

# Development: Design Qualification (DQ) Flow Diagram



# Development: Qualification for Cold Chain

- Performed to demonstrate the robustness of the transportation procedure.
- The TR uses “qualification” to replace the term “validation”.
- Qualification is more in line with shipping studies as we cannot “validate” the “weather” or the “human factor” involved in such activities involved in the transportation of temperature sensitive medicines.

# Development: OQ and PQ

- **Approach taken in the TR was to be consistent with FDA's Process Validation guidance. ("Why re-invent the wheel ?")**
- **Operational Qualification**
  - **Simulated testing that incorporates a challenge; ie, controlled chamber test in a lab.**
- **Performance Qualification**
  - **Field testing using the packaging system as it will be regularly used.**

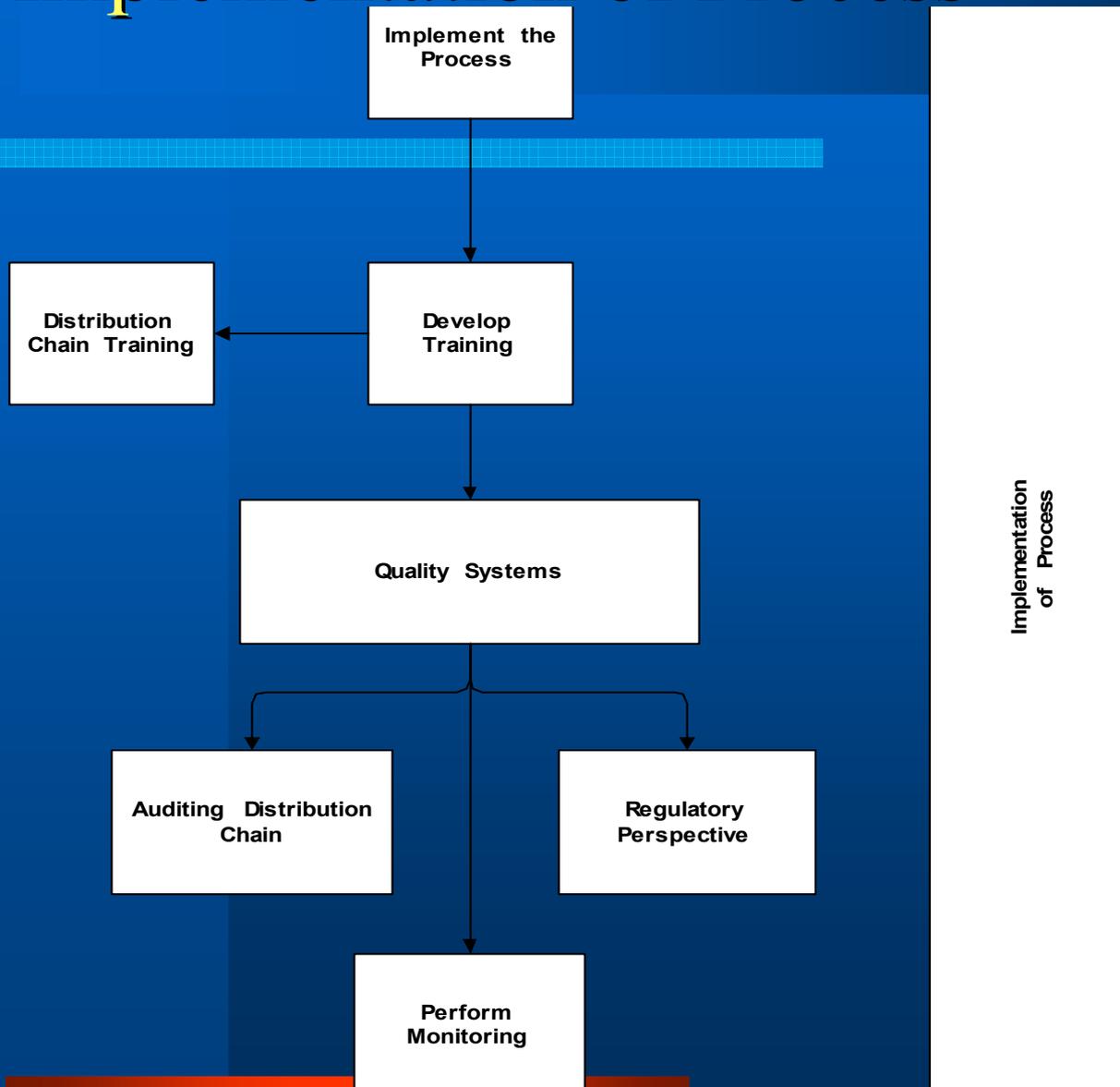
# Development: OQ should include

- **Exposure to expected temperature extremes**
- **Excess time duration**
- **Min and Max defined configurations**
- **Thermal mapping of the container with load (if not performed in the DQ)**
- **Calibrated temperature monitors**
- **Sufficient replicate tests**

# Development: PQ should include

- **Field Shipments**
- **Representative of “Real World” shipments**
- **Consecutive tests to show reproducibility**
- **Seasonal testing should be considered**
- **Representative product may be used**
- **Monitoring locations selected in OQ studies**

# Detailed discussion of TR 39: Implementation of Process



# Implementation: Training

## Target Audiences

- **Product Stability Organizations**
- **Manufacturing**
- **Quality Organizations**
- **Regulatory Organizations**
- **Packagers / Engineering**
- **Distribution**
- **Forwarders & Carriers**
- **Product & Service Providers**

# Implementation: Quality Systems

- Approved written procedures and specifications
- Calibration Program
- Stability Program
- Qualification Program
- Deviation & Investigation Program
- Corrective/Preventive Action Program (CAPA)
- Training Program
- Audit Program
- Monitoring of Transportation Data
- Change Control Program

# Audit Transport Providers ?

## Non – Approved Carrier



# Carrier Qualification Needed ?

Non - Approved Carrier or Bad Hair Day



# Implementation: Auditing

- Walk the Distribution Chain
- Know Your Product Requirements
- Are GMPs Being Adhered to?
- Ensure Distributor Deficiencies are Being Tracked and Completed per Post-Audit Commitments

# Continuous monitoring and improvement of your cold chain

- MONITOR: Temptale/other monitor data
- CORRELATE: Temptale data with Qualification and Specifications.
- EVALUATE: Periodic historic temp/time data- product vs ambient Temptales.
- REQUALIFY: Container, shipping configuration, route, revise specs.

# Conclusion

- **Cold Chain- Final Thoughts**
- **Acknowledgements**
- **Questions /Comments**

# Cold Chain- Final Thoughts

- “Lets start at the End (a.k.a. the patient is waiting)” - Dr. Ed Kaminski (VP Global Compliance Ops, Wyeth)
- Routine Monitoring with Temp Tale  
Example: 2003 Statistics for Wyeth:  
51 deviations / 4649 shipments ~ 1%
- Is that good enough ?

# Final Thoughts...

- **If 99 percent is good enough then:**
  - **2 million documents will be lost by the IRS this year !.**
  - **2 plane landings daily at O'Hara Intl Airport, Chicago will be unsafe !.**
  - **20,000 incorrect drug prescriptions will be written in the next 12 months !.**
  - **107 incorrect medical procedures will be performed by the end of the day today !.**

# Acknowledgements

- **PCCDG Team**
- **Rafik Bishara (Eli Lilly / Sensitech)**
- **Don Wilson (Amgen)**
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- **Ed Smith (Wyeth)**
- **NEPDA Committee – Louis Zaczekiewicz, Jerry Boudreault**

# Thanks for Listening –Questions?

## Cold Chain Management

