Agenda

1. Background, Scope and Purpose

2. Strategic Consideration for Temperature Excursion & Transportation Studies

3. Design and Conduct Transportation Study

4. Apply Transportation Study Results to Quality System
Terminology

**Excursion:**

Temperature and other environmental conditions experienced by products outside of the registered specified ranges.

**Transportation study:**

Study conducted to assess the effects of transportation on the drug product, drug substance and excipient based on the knowledge of the condition of transport (e.g., duration of transport, expected temperatures during transport and distribution, humidity, vibration, etc.). Conditions tested include but are not limited to thermal cycling or stress at elevated temperature.
Terminology

- **Stable Products:**
  Products not sensitive to environmental changes (e.g., metallic stents)

- **Sensitive Products:**
  Products with certain sensitivity to environmental conditions and that have to be protected during transportation (e.g., most of the pharmaceutical, biological and combinational products)

- **Highly Sensitive Products:**
  Products having a limited range of storage and transportation conditions. Excursion outside of these ranges is an actual cause of product deterioration (e.g., vaccines)
Types of Stability Studies

- Studies on In Process Material
- Studies on Product Storage
- Studies on Product Shipping
Background

**Why is transportation study important?**

If temperature sensitive products are not adequately protected during the transport, drug product may degrade and lose therapeutic value, other detrimental consequence might also occur.

*Regulatory Guidance:*

There are no specific guidelines like ICH Q1A-D for testing to determine the suitability of the transportation conditions for temperature sensitive products.
The presentation will focus on the transportation studies and distribution of:
- Sensitive products
- Highly sensitive products

Stable products are outside of scope of this talk.

Temperature excursion during transportation is the main focus of the presentation.
Purpose

To share the strategy and stability program for

- Designing transportation study to determine optimal transport conditions that ensure product quality, as well as cost effective and practical distribution.

- Use technical data and scientific rationale to support the product transportation policy and quality system
Get Global Picture Before Designing Transportation Studies
Strategic Consideration in Designing Transportation Studies

Transportation Study Design

Product  Ware House  Distribution Chain  Compliance  Cost
Product Consideration

Product Knowledge

- Stress study
  - Acid
  - Base
  - Oxidation
  - Thermal
  - Photo
- Previous R&D stability
  - Long term &
  - Accelerated

Inputs for Transportation Study

- Temperate
- Temperature range
- Duration
Are the warehouse temperature and humidity controlled and monitored?

How tight is the temperature and humidity controlled?

How is temperature and humidity monitored? How does the alarm system work?
Mapping Distribution Chain

Manufacturing site

Distribution Center

Distribution Center

Distribution Center
Distribution Chain Consideration

How is the product under consideration shipped from manufacturing site to distribution center?

How is the product shipped from DC to the user?

Is the product allowed to be returned to the DC?

Can the product be moved from account to account?

What kind of control is needed for distribution?
USP <1079> GOOD STORAGE AND DISTRIBUTION PRACTICES FOR DRUG PRODUCTS:
“The good storage and distribution should facilitate the movement of drug products throughout a supply chain that is controlled, measured, and analyzed for continuous improvements and should maintain the integrity of the drug product in its packaging during storage and distribution.”

FDA 21 CFR part 205:
“Each outgoing shipment shall be carefully inspected for identity of the prescription drug products and to ensure that there is no delivery of prescription drugs that have been damaged in storage or held under improper conditions.”
The Cost Factor

- $ of temp control in shipment
- $ of temp monitoring
- $ of out of compliance
- Product scrap
- $ of temperature control in storage
- $ of shipment

The Cost Factor: A pie chart illustrating the various cost factors involved in temperature control and monitoring, with each section representing a different cost category.
Cost Saving Recommendations

- Temperature control during shipment is usually very costly. If possible, conduct studies to support the broadest possible allowed temperature range during product shipment.

- If it is feasible, limiting the transit time is usually more economic than requiring temperature control shipment.
Weighing Temperature Control & Monitoring Options

**Temperature Control**
- Active Systems
- Passive Systems

**Temperature Monitoring**
- Temperature indicator
- Electronic data loggers

Ref: “Model requirements for the storage and transport of time and temperature sensitive pharmaceutical products”. WHO publication
Gaining Global View

- Take product, logistics (warehouse storage and distribution), compliance, cost and other factors into consideration when designing transportation studies.

- Explore the extreme of product thermal tolerance to lower the cost of temp control and monitoring during storage and shipping.
Design and Conduct Transportation Studies
Interactive Exercise 1

1. If you establish long term stability condition at 25°C/60% RH, would you place some control over distribution of product in zone I and zone II countries?  
   1a). If yes, what kind of control would you implement?  
   1b). If no, why?

2. If you establish long term stability condition at 25°C/60% RH, would you place some control over distribution of product world wide?  
   2a). If yes, what kind of control would you implement?  
   2b). If no, why?
Storage vs. Transportation Condition

- FDA has presented their view that transportation conditions may differ from storage conditions, provided the manufacturer presents satisfactory supporting data.*

- The Key is to present satisfactory supporting data

*FDA presentation in IBC Informa life sciences, 2006 & 2007
Know the Temperature Range

Temperature Range During Storage and Transportation

Mean Kinetic Temperature (MKT)
Approaches to Map Distribution Environment

- Study with packaged loaded with data logger
- UPS/Fedex Data
- Other publications
- Historical climatic data World wide*

* Note there is difference between climatic temperature data and actual shipping vehicle temperature
Mapping the Distribution Chain Environment
An Example of Temperature Range During Transportation

![Graph showing temperature excursion and stability studies over time in transportation for different locations.](image-url)
Mean Kinetic Temperature

- Recommended by USP to assess the effect of variable environmental condition on product quality and shelf life.

- Convert variable temperature into an equivalent steady temperature. The steady temperature is used to determine the effect of excursion.

- MKT is not an arithmetic average, but a calculation derived from Arrhenius Equation.

\[
MKT = \frac{\Delta H}{R} - \ln \left( e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n} \right) \tag{n}
\]

Where \( \Delta H \) is the heat of activation energy, and \( R \) is the gas constant.

\[ R = 8.3144 \times 10^{-3} \text{ kJ/mole/K} \]
Definitions

**Temperature Cycling Study:**
Studies in which the drug product, drug substance or novel excipient is repetitiously subjected to high and low temperatures.

**Thermal Stress Study:**
Testing conducted on the drug product, drug substance or novel excipient to generate decomposition products after exposure to specific stress condition (e.g., heat, light, humidity, acid, base and oxidative reagents or their combination).
Transportation Study Design

- To assess the effect of temperature fluctuation on product stability and shelf life
- The temperature range product experience during transportation is usually much high than at long term storage

Thermal cycling study

- If MKT \leq \text{long term storage temperature}, this study is not needed, use ICH stability study results
- If MKT > \text{long term storage temperature}, use intermediate and accelerated study results if they are supportive.

Thermal stress study at MKT

- Usually conducted at temperature greater than accelerated study temperature, with shorter duration
- May test multiple temperature points, the higher the temperature, the shorter the duration.

Thermal stress study at temp higher than MKT

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# Thermal Cycling Study

## Temperature Condition
- Freeze-thaw cycles, with the low and high ends temp. being the coldest & warmest temp. from the distribution chain (DC) environment temp. mapping
- Alternatively, the high end can be room temp.

## # of Cycles
- Typically 3
- Depends on the actual situation of transportation and DC logistics

## Duration of thermal cycles
- Residing time at each extreme temperature depends on actual shipping Situation, evaluate the worst case scenario.
- Allow enough time to reach temperature equilibrium.
Thermal Cycling Study

# of Lot Evaluated

- One lot
- May need to evaluate one lot per design per dose strength if these factors affect the study outcome

When to Conduct the Study

- Pre-market approval, after product design and manufacturing process finalized
- Can start during clinical phase

Attributes tested

- Same as stability study, should include physical, chemical, biological attributes if applicable
- Should include container closure system evaluation too.
Thermal Stress Study

Temperature Condition

- Usually conducted at temperature greater than accelerated study temperature.
- May test multiple temperature points.

Study Length

- Depends on the stability of the product and temperature point tested.
- Usually, the higher the temp., the shorter the study length.

# of Time Points

- Test at least 2 or 3 time points per temperature condition.
Thermal Stress Study

# of Lot Evaluated
- One lot
- May need to evaluate one lot per design per dose strength if these factors affect the study outcome

When to Conduct the Study
- Pre-market approval, after product design and manufacturing process finalized
- Can start during clinical phase

Attributes tested
- Same as stability study, should include physical, chemical, biological attributes if applicable
- Should include container closure system evaluation too.
Other Transportation Studies

Reference:
1. Guidelines for selecting and using ISTA test procedures and projects, ISTA
2. ASTM standards
Interactive Exercise 2

Through temperature mapping of the distribution chain environment, you find that your product will experience temperature outside of your registered long term storage temperature range during transit, you then conduct thermal cycling and thermal stress study to support distribution of product at temperature outside of long term storage temperature range, do you test the product at long term storage temperature till the end of shelf life after exposing to thermal cycling condition or thermal stress condition? Why?
“The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and the subsequent use.”
Apply the Transportation Study Results to Quality System
Interactive Exercise 3

Your thermal cycling study and thermal stress study results indicate that your temperature sensitive product can tolerate cycling between extreme temperature during transit and is stable for short period of time (e.g. 2 weeks) at temperature 20°C higher than your long term storage temperature, which of the following option will you prefer for distribution of product?

a) Control transportation environment temperature to protect the temperature sensitive product
b) Ship without temperature control but limit the transit time to minimize the thermal degradation
c) Use protective packaging and limit transit time to ensure quality of the product
d) Other
Establish Product Distribution Policy
- SOP
- DOPs

Conduct real time transportation validation study.

Establish Tracking System to ensure compliance to the company distribution requirements.
Establish Transportation and Distribution Process

Product Distribution

- Transportation study results
- Packaging study Results
- Distribution Requirements
- Cost of Transport Options
Establish Transportation and Distribution Process

Product Package Requirements

Determine:
- If thermostatic pack will be used
- Is it on individual product unit or a bulk container?
- Is temperature monitoring device needed on individual unit or bulk container?
- What kind of temp monitoring device will be used

Product Transit Requirement

Determine:
- Routes of transit
- If temp control transit is needed? If so, what kind of temp control and how to monitor the temp.
- Commercial carriers to be used, and specific quality agreement
- Can product be returned? How to handle product return?
- Can product be moved from one account center to another, how?

Transit Time Requirement

Determine:
- Should transportation time be limited
- If so, how long product can be in transit
A hypothetical product stability and transportation study result summary

<table>
<thead>
<tr>
<th>Temperature Range</th>
<th>Product Stability</th>
</tr>
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<tbody>
<tr>
<td>&lt;-20°C</td>
<td>Unknown</td>
</tr>
<tr>
<td>-20°C to 5°C</td>
<td>At least 3 months</td>
</tr>
<tr>
<td>5°C to 25°C</td>
<td>36 months</td>
</tr>
<tr>
<td>25°C to 30°C</td>
<td>6 months</td>
</tr>
<tr>
<td>30°C to 40°C</td>
<td>1 month</td>
</tr>
<tr>
<td>40°C to 50°C</td>
<td>3 days</td>
</tr>
<tr>
<td>50°C to 60°C</td>
<td>8 hrs</td>
</tr>
</tbody>
</table>

- Each of the temperature range is assessed separated
- Consider the cumulative effect of exposure to various temperature range during product transportation
Apply Safety Margin

- Besides considering the cumulative effect of exposure to multiple temperature range during transit, take the following into consideration when establishing product distribution process:
  - Seasonal climate change
  - Regional climate difference
  - Green house effect in the delivery truck without temperature control

- The transportation process should take into account of the worst case scenario
Transportation Validation Study

- Study conducted after establishing product distribution process.
- It is a real time study mimicking the entire product transit route from manufacturing site, to distribution center to end users.
- Include transit during hottest time of the year to the regions with highest temperature.
- Include longest route and max. transit time
- Preferably include temperature monitoring device for the study
- Test all the stability attributes as in storage and transportation stability studies
If temperature control is required, establish appropriate temperature monitoring system.

If there is limit on transit time, monitor product movement to ensure the time limit is not exceeded.
Conclusions

- It is acceptable to distribute product at conditions outside of long term storage condition, as long as the transportation condition is fully tested and that product quality is not compromised.

- Consider product intrinsic properties, distribution logistics/needs, transportation/packaging options, cost and compliance when conducting transportation studies.

- The product distribution process should be supported by the transportation study results.
Conclusions

- Transportation conditions have to be determined considering:
  - risk of product degradation
  - combined effect of various temperature range exposure or other hazardous environmental conditions
  - seasonal climate changes
  - regional climate difference.

- The controls implemented for product distribution should be adequately monitored and validated.
Temperature Excursions and Transportation Studies for Stability Program

**Revision History**

<table>
<thead>
<tr>
<th>Revision</th>
<th>Date</th>
<th>Description of Change</th>
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