Shipping and Transportation Studies to Evaluate Drug Product Quality

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Abstract — Many pharmaceutical or biotechnological products require transport using temperature-controlled systems to maintain their therapeutic properties. There are presently no official guidelines for testing pharmaceutical products in order to define suitable transport specifications established by the FDA. After reviewing the current guidance documents, this study proposes a methodology to define appropriate transport conditions, while trying to keep competitive cost. This design project aims to provide a guideline to develop and design shipping & transportation studies. The design will consider critical factors such as transit time, transit routes, environmental conditions to evaluate that there is no effect on critical quality attributes (i.e., appearance and stability indicating analytical tests) of the evaluated/shipped product.

Key Terms — Pharmaceutical Products, Temperature, Transport, Shipping & Transportation Studies.

INTRODUCTION & LITERATURE REVIEW

Maintaining the stability of drug substances and drug product is considered a GMP for pharmaceutical companies and the FDA. A major concern of the pharmaceutical industry and health authorities is to guarantee that drugs are delivered to patients without loss of therapeutic properties. Most products developed by the pharmaceutical, biotechnological or biologics industries require temperature controlled distribution channels, and it is not infrequent that delays during transport time's temperature cannot be maintained. The problem is that if this happens the drug may experience temperature excursions. Many of these products are sensitive to transport conditions; they need special care to ensure that their quality is not impaired by transport.

Regulatory authorities require that the manufacturer ensures product quality not only during storage or transport but until it is used for patient treatment. This requirement is a challenge for the manufacturer; since it must be ensured even after controls by the manufacturer in the supply chain have ended. Also, drug product manufacturer must decrease the risk of quality defects as much as possible. Quality defects can occur if the temperature chosen for transportation is outside the registered temperature range. This could also happen if the transportation company fails to ensure the specifications given. The manufacturer must balance both situations by choosing a good distribution plan.

The economic part is an additional factor for all this manufacturers because business must be rentable. Choosing the distribution plan is as important to the manufacturer. The concern is high because if the lot is damaged it can't get revenue and all the investment might be lost or the product can be sold damaged and the image of the company will get affected, plus lawsuits will be the future.

There are no guidelines for testing to determine the suitability of transport conditions for sensitive products. A study from the different climatic zones will be accomplished to know best routes possible and suitable package. This will determine optimal transport condition (i.e., air, sea, road) and transit time (i.e., daily, weekly, monthly) to provide product protection. Therefore, manufacturing companies must provide protocols, data and reports to demonstrate that the drug product critical quality attributes are not affected during the shipping & transportation process.

REGULATIONS AND GUIDELINES

ICH-WHO, summarized information below: ICH Q1A (2.1.2) (1)-WHO (2.1.2) (7) gives general guidance on how to perform stress tests. The results

of such tests are essential to determine the sensitivity of a drug substance to temperature, humidity, oxidation, pH and light. The results of the stress tests are directly useful when it comes to transporting the drug substances, and will help to determine appropriate tests to control transport conditions for the drug product [1].

- ICH Q1A also describes the recommended conditions for performing long term and accelerated stability tests on drug substances and drug products, and gives useful guidelines on the temperature and humidity conditions for running these tests [1].

- ICH Q1A is similar to WHO glossary: Accelerated testing: studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes [1].

- ICH Q1A chapter 2.1.7; similar to WHO 2.1.7: Data from accelerated stability studies can be used to evaluate the effect of short term excursions higher or lower than the label storage conditions that may occur during the shipping of drug products [1].

- ICH Q1A chapter 2.1.7.3; same to WHO 2.1.7.3: Drug substances intended for storage in a freezer: testing on a single batch at an elevated temperature (5°C±3°C or 25°C±2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling [1].

- ICH Q1A chapter 2.2.7.5, similar to WHO 2.2.6.5: Drug products intended for storage in a freezer: In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (5°C±3°C or 25°C±2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition [1].

-ICH Q5C (6): Stability of biotechnological/biological products section 6.3. Accelerated and stress conditions: Studies under stress conditions may be useful in determine whether accidental exposures to conditions other than those proposed (during transportation) are deleterious to the product [2].

These guidelines conclude that the manufacturer can use the accelerated stability data to assess the significance of temperature excursions outside the standard conditions during transport.

- Food and Drug Administration (FDA), their view is that transport conditions may differ from storage conditions.

PRODUCT STABILITY

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The shelf lives of biotechnological/biological products may vary from days to several years. Thus, it is difficult to draft uniform guidelines regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological/biological products. With only a few exceptions, however, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf lives in that range. This takes into account the fact that degradation of biotechnological/biological products may not be governed by the same factors during different intervals of a long storage period.

When shelf lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter [2].

For products with proposed shelf lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter [2].

While the testing intervals listed above may be appropriate in the pre-approval or pre-license stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol, which supports elimination of specific test intervals (9 month testing) for post-approval/post-licensure, long-term studies.

Stability studies on active substances and packaged dosage forms are conducted by means of real time, long term tests at specific temperatures and relative humidity representing storage conditions experienced in the distribution chain of climatic zones of the country or region of the world concern. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will both reflect the results of the real time storage tests and allow for expected seasonal excursions of temperature.

Controlled Room Temperature

Controlled room temperature delineates the allowable tolerance in storage circumstances at any location in the chain of distribution. This also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at controlled room temperature or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. The common international guideline for long-term stability studies specifies 25°C±2°C at 60%±5% relative humidity, sampling intervals (frequency): 0, 3, 6, 9, 12, 18, 24, 36 months, minimum data requirements for submission: 12months. Accelerated studies are specified at 40°C±2°C at 75%±5% relative humidity, sampling intervals (frequency): 0, 3 and 6 months, minimum data requirements for submission: 6 months. Intermediate condition stability studies (if significant changes occur in accelerated condition) are specified at 30°C±2°C at 65%±5% relative humidity, sampling intervals (frequency): 0, 3, 6 months, minimum data requirements for submission: 6 months. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage in storage conditions in addition to the excursions allowed by controlled room temperature. The term room temperature is used in different ways in different countries, and for products to be shipped outside the continental U.S. it is usually preferable for product labeling to refer to maximum storage temperature or temperature range in degrees Celsius.

Bulk Product Stability

It is important that stability of the drug product from a physical-chemical standpoint is not compromised during the shipping and transportation process. This section provides an evaluation of typical stability considerations. Capacity of a formulation to maintain its specifications in a pre-determined packaging configuration:

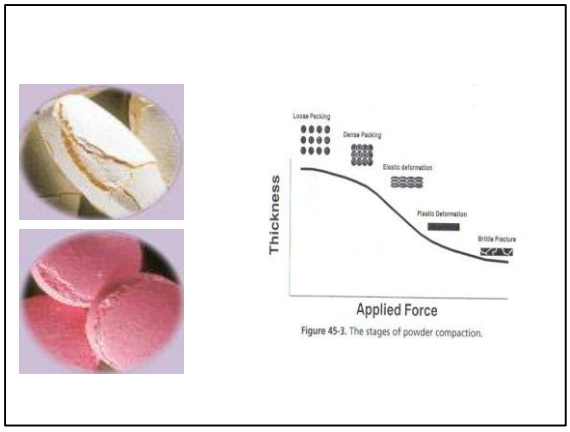

Figure 1
Physical Stability

1. Physical stability complaints:
    - Broken product within primary package.
    - Color variation in product.
    - Edge erosion in product.
    - Product identity issues.

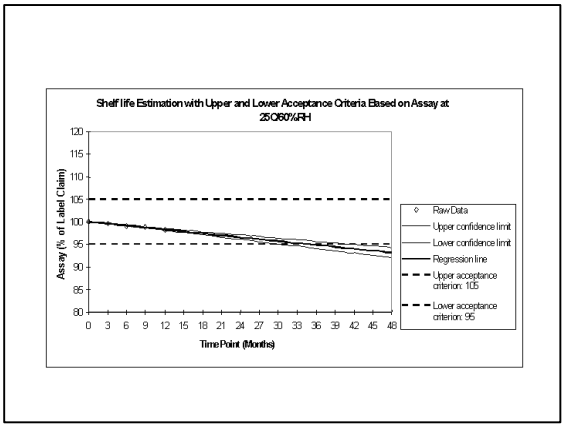

Figure 2
Chemical Stability

2. Chemical stability complaints:
    - Lack of efficacy
    - Upon drug product administration, patient experiences and secondary or adverse event. Clinical safety.
    - During stability studies critical stability indicating attributes are below/above specification limits.

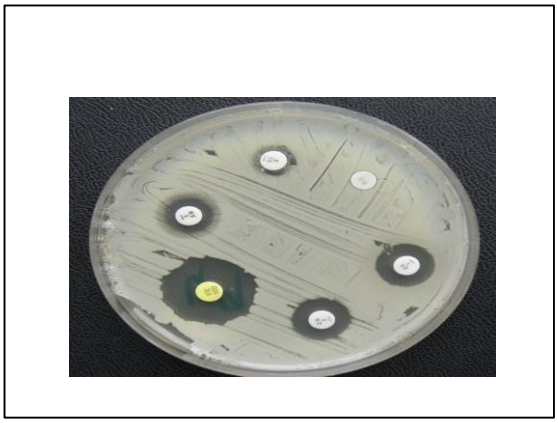

Figure 3
Microbiological Stability

3. Microbiological stability complaints:
    - Unusual odor in drug product.
    - Visible microbiological growth.
    - Secondary or adverse events. Clinical safety.

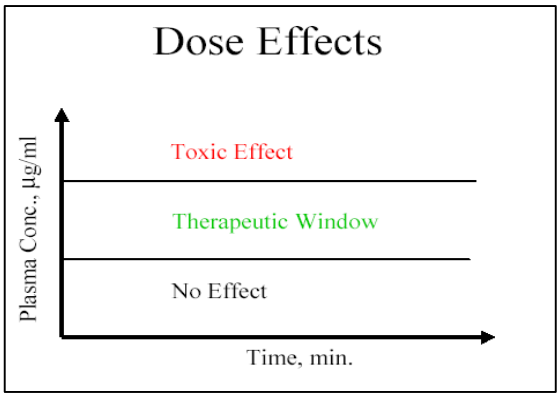

Figure 4
Therapeutic Stability

4. Therapeutic stability complaints:
    - Intoxication.
    - Lack of therapeutic effect.
    - Secondary effects.

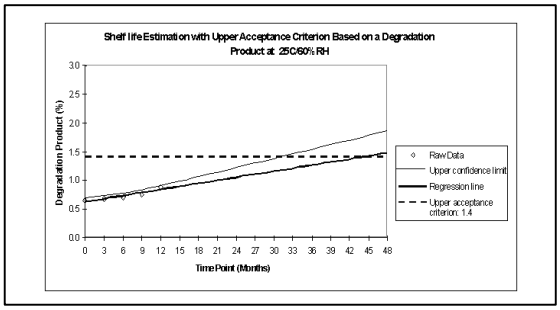

Figure 5
Toxicological Stability

Critical Aspects:

All degradation paths/mechanisms and degradation products/impurities must be pre-defined, studied and considered prior to recommending packaging configurations and shipping and transportation methods.

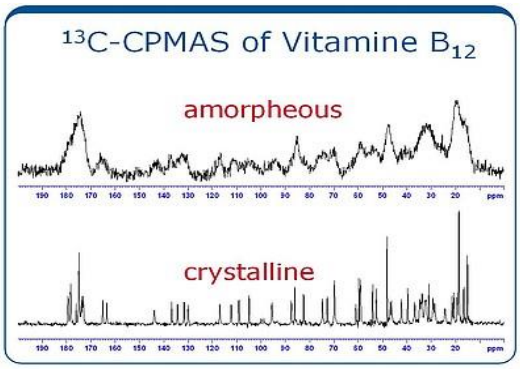

Figure 6
API Stability

API stability evaluates:

- Possible degradation paths/ mechanisms.
- Sensitivity to humidity, temperature, oxygen, interaction, pH, polymorphism.

Chemical degradation mechanisms/paths are classified:

- Oxidation: Addition or removal of oxygen or hydrogen.
  - It requires a small amount of oxygen to start a chain reaction.
  - Nitrogen or Carbon Dioxide is used to displace air in shipping and pharmaceutical containers to minimize degradation thorough oxidation pathways.
  - The oxidation "rate" is typically influenced by temperature, radiation or catalyst presence.
  - Oxidation could be inhibited with antioxidants: Ascorbic acid, Sodium Sulfite
- Hydrolysis: Typically in drugs containing "Esters" or "Amides".
  - The hydrolysis "rate" is influenced by temperature, humidity and solution pH.
  - When hydrolysis occurs, the API concentration reduces while degradants/impurities concentration increases.
  - Surfactants such as "Sodium Lauryl Sulfate" are added to stabilize the drugs.
- Racemization": APIs that contain a mixture of "dextro" o "levo" forms of the compound.
  - Frequently the "levo" form is more active from a pharmacological standpoint than the "dextro" form.
  - Stability depends on temperature, solvents, catalysts and presence or absence of light.
- Photochemical reactions: When drugs are chemically affected by radiation or specific wavelength [3].
  - Ultraviolet radiation is the principal cause of these degradation reactions.
  - Packaging configurations with colors are used for protection:
    i. Yellow or green for ultraviolet region.
    ii. Amber, good for ultraviolet region, poor protection for infrared region.

Packaging

A packaging component means any single part of a container closure system. Typical components are containers (ampules, vials, bottles), container liners (tube liners), closures (screw caps, stoppers), closure liners, stopperover seals, container inner seals, administration ports (on large volume parenterals (LVPs)), overwraps, administration accessories, and container labels. A primary packaging component means that is or may be in direct contact with the dosage form. A secondary packaging component means that is not and will not be in direct contact with the dosage form.

A container closure system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product [4].

- An effective bulk packaging configuration should protect the drug product from:
  - Foreign solids
  - Potency loss or degradant/impurity increase
  - Contamination
- Physical/Packaging factors:
  - Temperature
  - Light
  - Humidity
  - Vibration
  - Physical stress/compression
  - Transit times

Table 1
Example of Transportation Categories

Transport Category	Transport Conditions	Alt. Short-Term Transport (≤ 1 day)
Deep Freeze (Frozen)	≤ - 15 °C	≤ 5 °C
Frigo (Refrigerated)	2 – 8 °C	≤ 25 °C
Cool (Refrigerated)	2 – 8 °C	≤ 30 °C

Tempcontrol (≤ 30 °C)	≤ 30 °C	≤ 40 °C
Normal (none)	≤ 40 °C	≤ 50 °C

Ambient shippers alone may not offer sufficient protection during flight. Air temperatures will drop to sub-zero temperature. Depending on sample type, further thermal protection may be required in order to reduce variability, and this may be further affected by the season. Various products can offer thermal protection and may include gel materials, foam materials, or other products.

Refrigerated shipments can be protected by the use of materials that can be frozen or refrigerated prior to shipment, and this may vary according to the season as well.

When shipping frozen (dry ice) samples, the packaging container should be large enough to add dry ice for the duration of the shipment with a margin of safety (recommend 72 hours) and be evaluated in conjunction with a typical sample shipment size. Dry ice is available as pellets or blocks. Block ice will provide more longevity. If block ice is used, any vacant space can be filled with packing material or wadded paper to slow evaporation and cushion the samples. If pellet ice is used, place a layer of dry ice lining the bottom of the shipper, and then add samples, followed by additional dry ice to fill the chamber.

CLIMATIC ZONES

- Zone I: (21°C; 45%RH)
- Zone II: Subtropical, high humidity. (25°C; 60%RH)
- Zone III: Hot and dry. (30°C; 35%RH)
- Zone IV: Hot and Humid. (30°C; 70%RH)

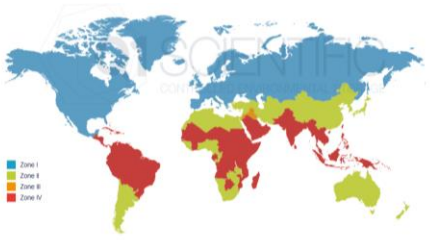

Figure7
Climatic Zones/Environment

Climatic Zone / Countries	Calculated data Temp. °C	MKT °C	humidity % r.h.	Derived data Temp. °C	humidity % r.h.
Climatic Zone I "Temperate" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	20	20	42	21	45
			Storage condition acc. to ICH Q1A: 25°C / 60%		
Climatic Zone II "Mediterranean, Subtropical" Japan, United States, Southern Europe	21,6	22	52	25	60
			Storage condition acc. to ICH Q1F: 30°C / 65% r.h.		
Climatic Zone III "Hot, dry" Iran, Iraq, Sudan	26,4	27,9	35	30	35
Climatic Zone IV "Hot, humid" Brazil, Ghana, Indonesia, Nicaragua, Philippines	26,7	27,4	76	30	70

Figure 8
Climatic Zones [5]

METHODOLOGY

Evaluation of ICH shipping and transportation

- Packaging configuration.
- Pre-defined transportation route and transit time.
- Environmental conditions (temperature and relative humidity) during transportation process.
- Impact evaluation on physical and chemical critical quality attributes.

Shipping and Transportation QRM

- Quality risk management prior to bulk shipping studies
  - ➢ Development of a QRM to document the current shipping and transportation processes, evaluation of potential risks, and prioritization of risk mitigation action plan/measures.

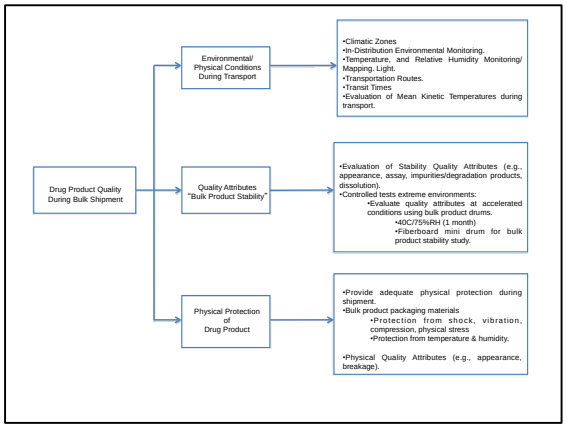

Figure 9
Bulk Shipping CTQ Diagram

Mean Kinetic Temperature

MKT is defined as the single temperature at which the total amount of degradation within a period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an Isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations [6].

Is a simplified way of expressing the overall effect of temperature fluctuations during storage or transit of drug products?

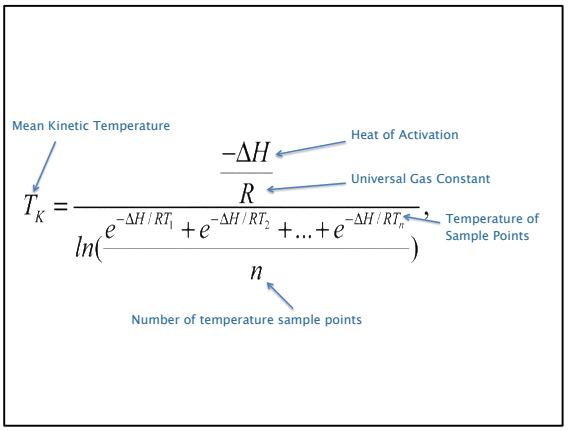

Figure 10
Mean Kinetic Temperature

ANALYSIS

The environmental conditions are described below:

The transportation routes as defined by climatic zones are also comparable to retrospective temperature and humidity mapping, as follows:

- Departure Location (Puerto Rico):
  - Climatic Zone IV: Hot and humid climate, (30°C/70%RH).
  - Similar departure location climatic zones between retrospective evaluation and current (Puerto Rico).
- Receiving Locations for Retrospective Evaluation (U.S.A.: Pennsylvania, Tennessee, California):
  - Climatic Zone II: Subtropical and Mediterranean climates, (25°C/60%RH).
  - Similar receiving location climatic zones between retrospective and current (U.S.A.).

Quality Attributes:

- Bulk product stability studies have been conducted for the drug products to evaluate the effect of accelerated environmental conditions (40°C/75%RH) on drug product quality attributes.
- These studies were conducted using unsealed polyethylene (PE) bags contained in a fiber mini-drum at 40°C/75%RH for 1 month.

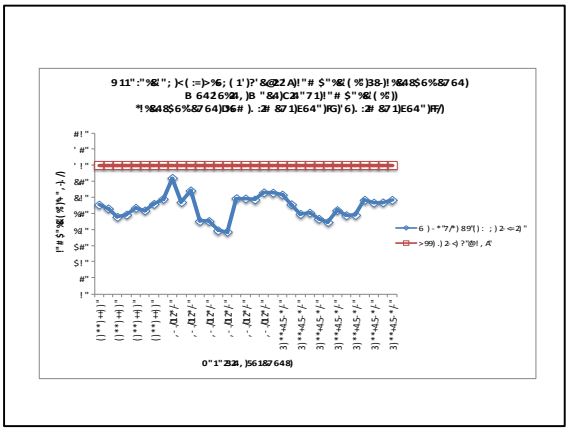

Figure 11
QRM Case Study

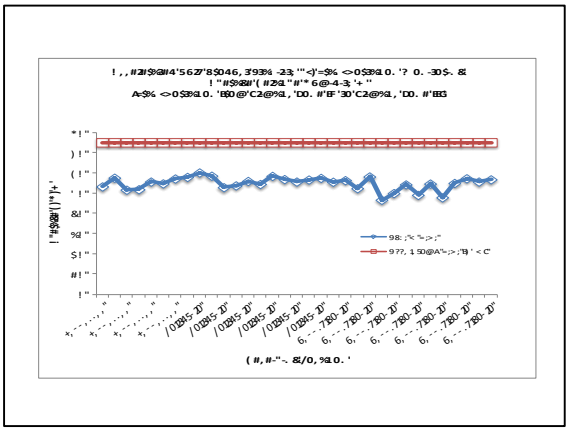

Figure 12
QRM Case Study

In the previous case study evaluate the QRM and new risk factors (Severity, Occurrence, Detection) if the transportation routes, climatic zones are kept equal when compared to case study, but it is noticed that there is no bulk product stability data available. You can select arbitrarily the ranking

number for severity, occurrence and detection, but in the right direction.

Table 2
Risk Scenario

Risk Scenario	Risk Factor			Risk Priori Number (RPN)
	Severity	Occurrence	Detection	
Environmental Conditions During Transport	6 Marginal	4 Moderate	5 Moderate	120
Quality Attributes During Transport	6 Marginal	4 Moderate	5 Moderate	120
Physical Protection of Drug Products During Transport	6 Marginal	4 Moderate	5 Moderate	120

Table 3
Risk Acceptability

RPN	Severity			
	Negligible	Marginal	Critical	Catastrophic
501-1000	Cannot achieve this rating	Intolerable	Intolerable	Intolerable
100-500	ALARP	ALARP	Intolerable	Intolerable
51-99	Broadly Acceptable	ALARP	ALARP	ALARP
1-50	Broadly Acceptable	Broadly Acceptable	ALARP	ALARP

Note:
ALARP = "As Low As Reasonably Practicable"

STRATEGY & RESULTS

Risk Control Strategy:

- Shipping Studies to evaluate:
  - Effect of environmental conditions, transit route, and transit time on critical quality attributes.
  - Testing of stability indicating analytical tests
  - 3 lots in winter, 3 lots in summer (commercial lots)
- To show no impact of past and current shipping methods:
  - If fluctuations occur, this will allow the establishment of these tolerances with data analysis.
- Visual inspection:
  - The product will be visually inspected prior to shipment and after shipment at the receiving facility.
- Analytical and Micro Test:
  - The product will be analytical/micro tested prior to shipment and after shipment.
- Environmental data collection:
  - The study will collect environmental data of the Shipment while in transit from Puerto Rico to the receiving site.
- Analytical and Micro samples post-shipment:
  - The study will collect environmental data of the samples taken at the receiving facility while in transit to origin site.

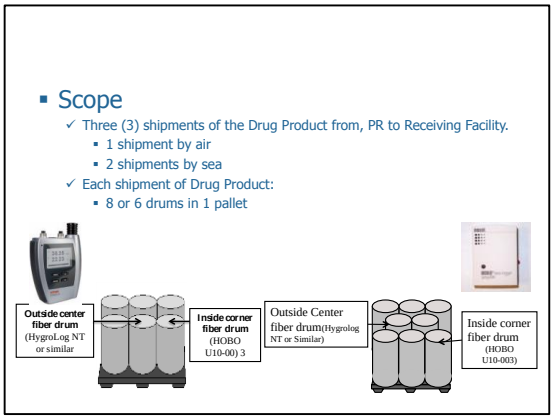

Figure 13
Strategy

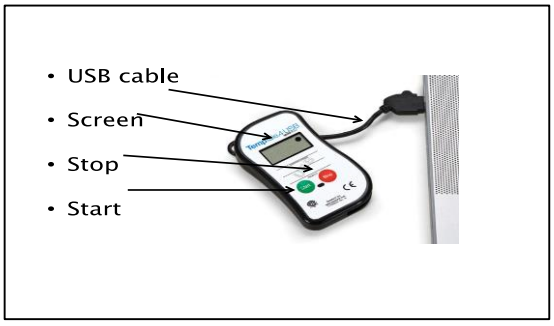

Figure 14
TempTale 4 USB

The TempTale®4 USB (TT4 USB) combines the industry-leading performance and reliability of our traditional TempTale4 temperature monitor with an enhanced feature set enabling quick and easy shipment dispositions. With its integrated USB 2.0 communications and powerful on-board microprocessor, the TT4 USB creates a secure Adobe® PDF format shipment report, without installing proprietary software or hardware readers on your computer.

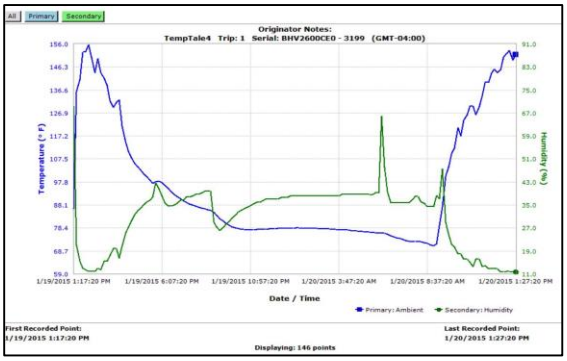

Figure 15
TT4 Graph Trip 1

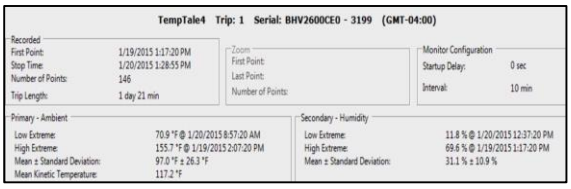

Figure 16
TT4 Readings Trip 1

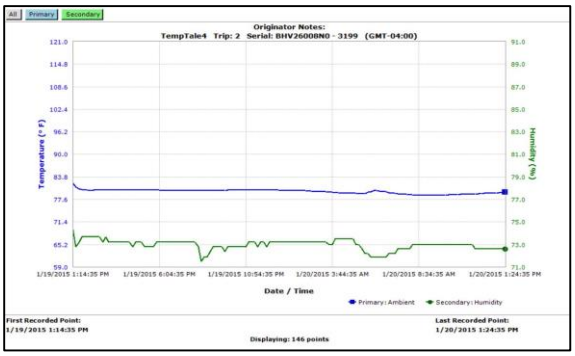

Figure 17
TT4 Graph Trip 2

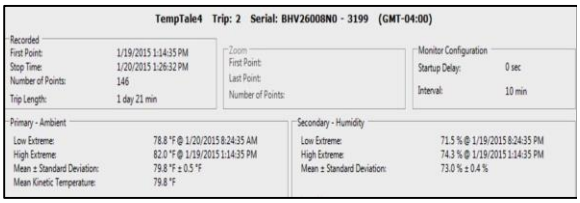

Figure 18
TT4 Readings Trip 2

Designed to compare in transit temperatures between fully loaded and empty trailer and sea containers. Shipment containers will be equipped with multiple TempTale 4 temperature monitoring devices, placed in a pre-determined pattern.

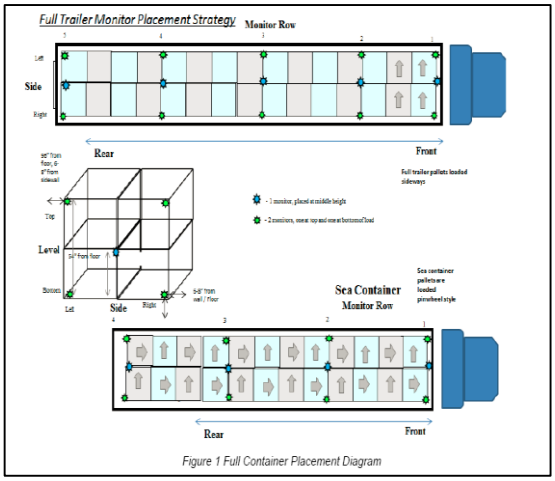

Figure 19
Full Trailers Monitoring

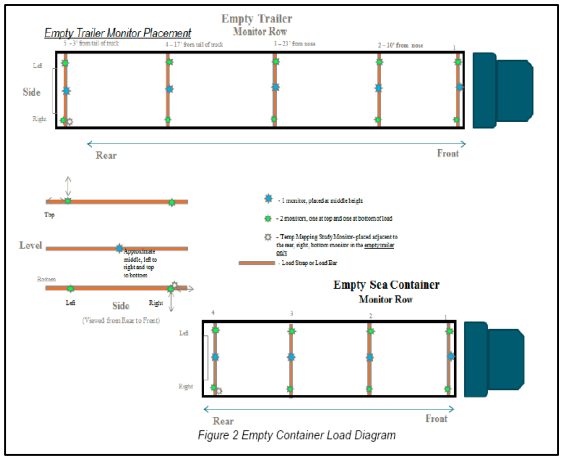

Figure 20
Empty Trailer Monitoring

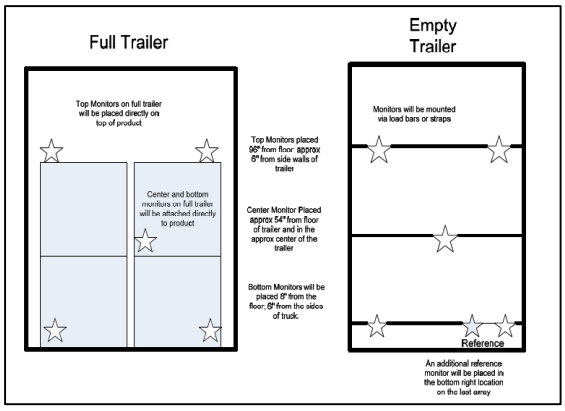

Figure 21
Trailers

Association studies will provide two sets of key temperature statistics for each shipment. The first will compare the monitor in the lower right-hand rear location, referred to as the reference location

herein, to all other locations in the empty trailer. Then all monitored locations in the empty trailer will be compared to the equivalent locations in the fully loaded trailer. This comparative temperature information can be used in analyzing Temperature Mapping Study Data.

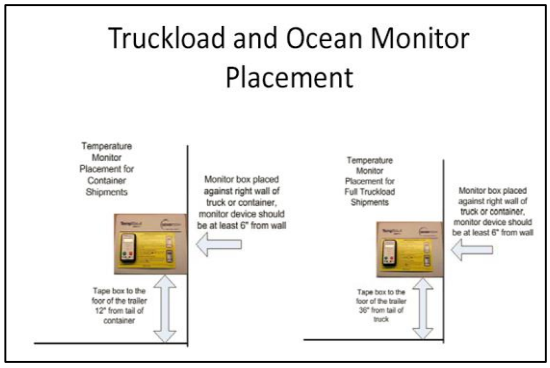

Figure 22
Monitors

Figure 23
Airplane Monitoring

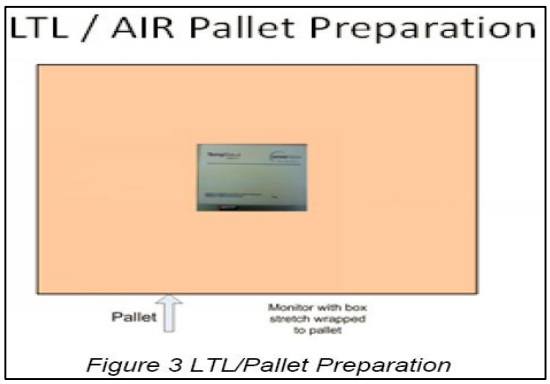

Figure 24
Pallet Monitoring

The project is designed as an effective means to collect temperature data in non-temperature controlled shipments. Shipments containers will be equipped with Temptale 4 temperature monitoring devices and will be sent via Ocean, Air, Full Truckload and Less than Truckload (LTL). The study is designed to allow for up to thirty shipments on each transportation lane in the summer and winter season.

CONCLUSION

The objective of this design project was achieved by providing a guideline to develop and design shipping & transportation studies. The design considered critical factors such as transit time, transit routes, and environmental conditions to evaluate that there is no effect on critical quality attributes (i.e., appearance and stability indicating analytical tests) of the evaluated/shipped product. The relationships of shipping and transportation factors and stability indicating quality attributes was evaluated and presented as an integration strategy between total quality management and the shipping & transportation process. With this approach the manufacturing facilities will be able to validate shipping & transportation processes, controls and procedures to maintain quality attributes throughout the supply chain & distribution.

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