Development of Bulk Shipping Studies in Pharmaceutical Industry

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Abstract *— A bulk shipping study in the pharmaceutical industry consists in monitoring and analyzing the environmental conditions (e.g. temperature and relative humidity) during shipping and transportation of the drug product. The environmental conditions could affect the drug product critical quality attributes such as identity, strength, quality, and purity. The Company X needs to ensure that the shipping process and transportation does not affect the product X quality attributes i.e., safety, efficacy, strength, integrity and purity. The proposed method for this design project is the implementation of data loggers with the product during the shipping and transportation process to record the environmental conditions. Also to ensure that critical bulk product quality attributes are not affected with the exposed environmental and shipping/transportation conditions.*

Key Terms *— Bulk Shipping Studies, Environmental Conditions, Mean Kinetic Temperature and Mean Relative Humidity.*

INTRODUCTION

Bulk shipping studies provide documented evidence of the current state for shipping/ transportation process of the Y Bulk Product shipped from Puerto Rico to the receiving facility in USA (Northeastern region). The shipping study includes the following: environmental monitoring and data collection (Temperature and Relative Humidity), sampling, testing and evaluation of drug product quality attributes (e.g., identification, particle size, assay, and dissolution) before and after the shipping/transportation and visual inspection of product and drums/pallet(s).

RESEARCH OBJECTIVES

The main objective of this project is to evaluate and analyze the environmental conditions during the shipping and transportation process of the product. Also to evaluate and ensure that handling, storage and distribution are adequate to maintain the product quality attributes: identity, strength, quality, and purity of the drug product [1][2].

RESEARCH CONTRIBUTIONS

The main contribution of this project is to provide the tools for the development of a shipping study experimental design in the pharmaceutical industry. Also an important contribution is to make recommendations about the good manufacturing practices of shipping and transportation process.

BACKGROUND INFORMATION

The shipping study was conducted in Summer Season which represents the worst-case environmental condition scenario (High temperature and high relative humidity). The shipments departure location is at the Climatic Zone IV Puerto Rico to the receiving location Climatic Zone II Pennsylvania (Refer to Table 1). A climatic zone is a region of the world in which the climate can be defined using a few key parameters and characteristics [1].

Table 1
Classification of Climatic Zones

Climatic Zone	Characteristics	Temperature	Relative Humidity
II	Mediterranean and subtropical climates.	25°±2°C	60% ± 5%
IV	Hot, humid climate, tropics.	31°C±2°C	70% ± 5%

The environmental data was evaluated by the use of the Mean Kinetic Temperature and average relative humidity [4]. Mean Kinetic Temperature (Refer to Equation (1)) is a calculated single temperature that is analogous to the effects of temperature variations over a period of time [3].

$$T_k = \frac{\Delta H / R}{-\ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)} \quad (1)$$

T_k= the mean kinetic temperature.

ΔH= the activation energy.

T_1 to T_n= the temperatures at each of the sample points.

R= the gas constant.

n= the number of temperature sample points.

Also the mean relative humidity (Refer to Equation (2)) was evaluated. Relative humidity is the amount of water vapor in a mixture of air and water vapor.

$$RHmean = \frac{\sum RH}{n} \quad (2)$$

RH= the mean relative humidity

$\sum$RH= the relative humidity at each of the sample points.

n= the number of relative humidity sample points.

The environmental conditions (Temperature and Relative Humidity) can affect the drug product stability. The stability consists in how the quality of a drug product varies with time under the contact of a variety of environmental conditions, such as temperature, relative humidity, and light. Also establishes a shelf life for the drug product and recommended storage conditions. The ICH's "Q1A: Stability Testing of New Drug Substances and Products," states that data from accelerated stability studies can be used to evaluate the effect of short-term excursions higher or lower than label storage conditions that may occur during the shipping of drug products [4][5].

RESEARCH METHODOLOGY

The shipping study includes at least two (2) shipments of the Y product, one (1) shipment via air and one (1) shipment via sea. In each shipment, a minimum of two (2) drums with product and a maximum of five (5) drums per pallet will be transported via air and sea from Puerto Rico to the receiving facility. Refer to Figure 1 for details of drums arrangement on the pallet(s).

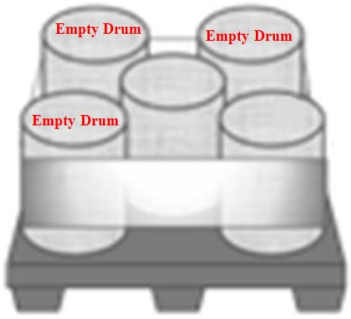

Figure 1
Drums Configurations

The shipping and transportation process for this study will be as per actual standard shipping process, without controlled environmental conditions. The Table 2 shows the minimum transit days by shipment type.

Table 2
Transit Days

Shipment Type	Days
Air	3
Sea	9

The Y product must be sampled before shipping process during the manufacturing process and sent to the laboratory for analytical testing.

The Y product will be visually inspected before and after the shipping and transportation process as per product appearance evaluation criteria described in Table 3. The visual inspection of the Y product must be done by inspecting the product inside the drum. The visual inspection must be performed on each drum with product.

Table 3
Product Visual Inspection

Acceptance Criteria
White to off-white particles, no visible lumps are present.

To monitor the temperature and relative humidity during the shipping and transportation process, two (2) calibrated data loggers will be used. Placed at the outside of a drum a HygroLog NT Data Logger and inside a drum and samples box a HOBO U10-003 Data Logger. These locations provide full monitoring of the environmental conditions inside/outside the drum(s). The HOBO U10-003 will be located inside one (1) polyethylene bag closed with a plastic tied wrap, to simulate the same shipping and transportation conditions of the Y product inside the fiber drum. This polyethylene bag must be placed over the closed polyethylene bag with product before closing the drum. The corner location in the pallet should represent the worst-case scenario since corner drums are more exposed to the surrounding environmental conditions. Refer to Figure 2 for details of the location of the device.

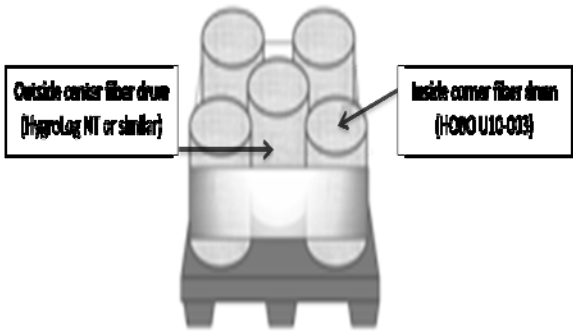

Figure 2
Data Loggers Location

The temperature and relative humidity conditions will be monitored and assessed by evaluation of the temperature and humidity profiles during the shipment process. Also, evaluation of temperature and relative humidity gradients between outside and inside of drums environmental monitoring, mean kinetic temperature (MKT) and mean relative humidity will be performed during transportation and their relation or effect on critical quality attributes as per product component specification method [4].

The drums and pallet(s) will be visually inspected before and after as per evaluation criteria described in Table 4. All drums/pallet(s) visual inspections must be conducted in GMP rooms (warehouse).

Table 4
Drums/Pallet(s) Visual Inspection

Acceptance Criteria
• Drums and pallet(s) must not have physical damage before and after shipping and transportation process. • Drums must be free of dents or rupture. • Drums seals must not be broken, damage, open or missing. • Drums must not have evidence of contact with water or another solvent. • No visible sign of condensation inside the drums.

The Y product must be sampled at the receiving facility. All samples must be taken in a room approved for sampling Two (2), four-ounce composite samples (i.e., representative sample from all drums containing product) of the product will be collected. Samples will be sent by next day delivery to Puerto Rico Laboratory for analytical testing. The same HOBO U10-003 data logger removed from the shipment will be placed inside the box with the samples to monitor the environmental conditions. Once the samples are received in the Laboratory one sample will be analyzed following the component specification method. The second sample will be kept (Laboratory) as contingency in case additional testing is required.

The Y product quality attributes will be evaluated before and after the shipping process and the product quality attributes are considered the study “responses” to be evaluated as the study acceptance criteria. If all quality attributes as per component specification method are acceptable before and after shipment, a summary of the shipping “factors” or environmental conditions during transportation (i.e., temperature and relative humidity) that supported the acceptable quality results will be performed and summarized. If any of the quality attributes “responses” do not meet the

acceptable criteria before or after shipment, then an evaluation of the shipping "factors" or environmental conditions during transportation will be performed to evaluate if any shipping and transportation environmental condition excursion is correlated to the impact on drug quality attributes.

RESEARCH RESULTS

The shipping study collects environmental data using a calibrated HOBO U10-003 Temperature/ Relative Humidity Data Loggers (inside the drum). Also a calibrated HygroLog NT (attached to the outside of a drum), providing full monitoring of the environmental conditions inside/outside of the drum per shipment. Refer to Table 5 below for elapse time of each shipment.

Table 5
Shipping Elapsed Time (Transit Time)

Method of Transportation	Shipment date from PR	Received date at US	Elapsed Time (days)
Air	08/17/2012	08/21/2012	3.80
Sea	08/17/2012	08/31/2012	14.00

Shipment product was sampled at the receiving facility in US and the samples were sent to Puerto Rico for analysis at the Laboratory. The samples were sent to PR via air next day with a calibrated HOBO U10-003 Temperature/Relative Humidity data logger inside the sample box. All quality attributes as per Material Specification were on acceptable conditions. The product quality attributes were evaluated before and after the shipping process and the product quality attributes were considered the critical study "responses". All quality attributes as per Material Specification were acceptable before and after shipment. Refer to Tables 6 and 7 below for a summary of results.

Table 6
Analytical Results – Air Shipment

Test	Acceptance Criteria	Before	After
Identification for RT Ratio	0.9 to 1.1	1.0 Ratio	1.0 Ratio
Identification (TLC RF Ratio)	0.9 to 1.1	1.0 Ratio	1.0 Ratio
Assay for Y product HCL	90.0 to 110.0	98.0 %	98.2 %
Assay for Y product N-Oxide	Less, Equal to 0.5	0.2 %	0.3 %
Dehydro-Degradant (DH)	Less, Equal to 0.2	0.1%	0.1%
Residual Solvent: Acetone	Less, Equal to 2000	486 PPM	713 PPM
Residual Solvent: Methanol	Less, Equal to 100	10 PPM	18 PPM
Dissolution Rate STGI Summary	Greater, Equal to 85	91% Min	89% Min
Particle Size 20 Mesh	Less, Equal to 10	0% ON	1% ON
Particle Size 40 Mesh	Less, Equal to 35	10% ON	17% ON
Particle Size PAN	Less, Equal to 30	5% ON	2% ON

Pass Fail

Table 7
Analytical Results – Sea Shipment

Test	Acceptance Criteria	Before	After
Identification for RT Ratio	0.9 to 1.1	1.0 Ratio	1.0 Ratio
Identification (TLC RF Ratio)	0.9 to 1.1	1.0 Ratio	1.0 Ratio
Assay for Y product HCL	90.0 to 110.0	98.0 %	97.3 %
Assay for Y product N-Oxide	Less, Equal to 0.5	0.2 %	0.3 %
Dehydro-Degradant (DH)	Less, Equal to 0.2	0.1%	0.1%
Residual Solvent: Acetone	Less, Equal to 2000	486 PPM	594 PPM
Residual Solvent: Methanol	Less, Equal to 100	10 PPM	13 PPM
Dissolution Rate STGI Summary	Greater, Equal to 85	91% Min	89% Min
Particle Size 20 Mesh	Less, Equal to 10	0% ON	1% ON
Particle Size 40 Mesh	Less, Equal to 35	10% ON	10% ON
Particle Size PAN	Less, Equal to 30	5% ON	16% ON

Pass Fail

Visual inspection of the product was performed before and after each shipment at Puerto Rico and US facilities respectively. The visual inspection included appearance inspection of the product inside each drum. Refer to Table 8 and Table 9 for a summary of the visual inspections. During the study all shipments complied with the product appearance criteria.

Table 8
Visual Inspection of Product, Drums/Pallets – Air Shipment

Test	Acceptance Criteria	Before	After
Visual Inspection of the product.	White to off-white particles, no visible lumps are present.	Pass	Pass

Table 9
Visual Inspection of Product, Drums/Pallets – Sea Shipment

Test	Acceptance Criteria	Before	After
Visual Inspection of the product.	White to off-white particles, no visible lumps are present.	Pass	Pass

Visual inspection of the drums/pallets was performed before and after each shipment at Puerto Rico and US facilities respectively. The visual inspection included verification that drum/pallet(s) did not have any physical damage before and after shipping/transportation. Refer to Table 10 and 11 for a summary of the visual inspections.

Table 10
Visual Inspection of Product, Drums/Pallets – Air Shipment

Test	Acceptance Criteria	Before	After
Visual Inspection of Drums/Pallets	Drums/Pallet(s) must not have Physical damage. Drums must be free of dents or rupture. Drum seals must not be broken, damage, open or missing. Drums must not have evidence of contact with water or another solvent. No visible sign of condensation inside the drums.	Pass	Pass

Table 11
Visual Inspection of Product, Drums/Pallets – Sea Shipment

Test	Acceptance Criteria	Before	After
Visual Inspection of Drums/Pallets	Drums/Pallet(s) must not have Physical damage. Drums must be free of dents or rupture. Drum seals must not be broken, damage, open or missing. Drums must not have evidence of contact with water or another solvent. No visible sign of condensation inside the drums.	Pass	Pass

The study was conducted in Summer Season from Puerto Rico to US (Northeastern Region) to have high temperature and a high relative humidity environment conditions. Since all analytical results were acceptable, a summary of the shipping "factors" or environmental conditions during transportation (i.e., temperature and relative humidity) that supported the acceptable quality results was performed and summarized (Refer to Table 12 below).

The environmental data was evaluated by the use of the mean kinetic temperature and average relative humidity. Mean Kinetic Temperature is a temperature that is useful in the evaluation of the impact of heat on pharmaceutical products [4][5].

Table 12
Monitoring of Environmental Conditions

Method of Transportation		MKT (°C)	Min (°C)	Max (°C)	Mean RH%	Min RH%	Max RH%
Air	Inside	30.30	20.62	45.45	58.58	51.37	78.62
	Outside	33.26	19.46	53.55	53.55	38.87	70.22
Sea	Inside	29.93	22.14	39.28	63.09	54.97	71.17
	Outside	30.12	22.98	42.63	60.63	41.14	68.89

The following graphics illustrate the environmental conditions (Temperature and Relative Humidity) during the shipping transportation process for air and sea shipments from Puerto Rico to US (Refer to Figures 3 to 10).

MKT: 30.30°C MAX: 45.45°C
Min: 20.62°C Transit Time: 3.80days

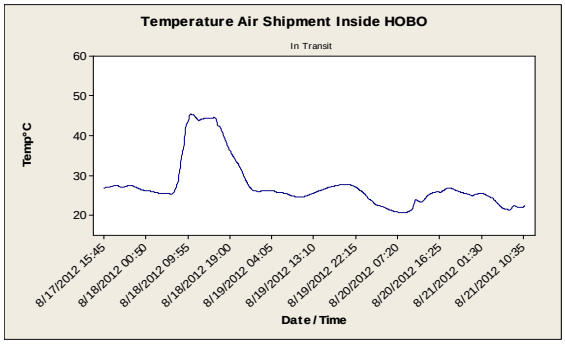

Figure 3
Temperature Air Shipment Inside HOBO

MKT: 33.26°C MAX: 53.55°C
Min: 19.46°C Transit Time: 3.80days

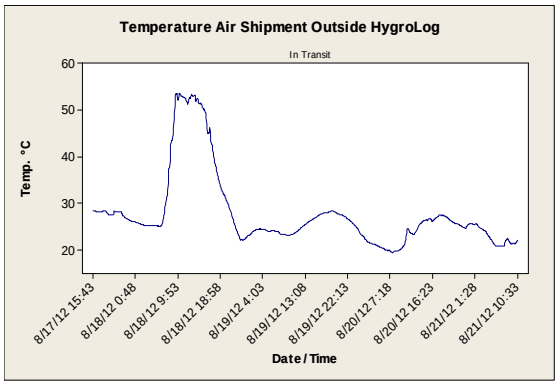

Figure 4

Temperature Air Shipment Outside HygroLog

MKT: 29.93°C MAX: 39.28°C
Min: 22.14°C Transit Time: 14.00days

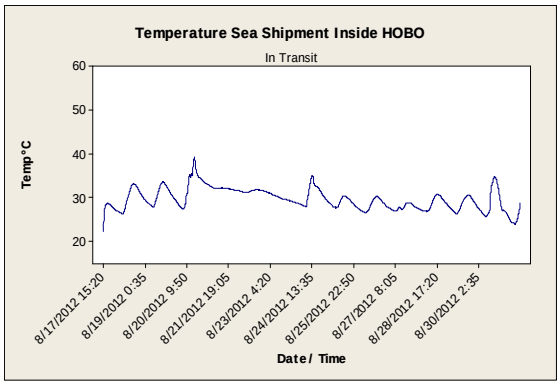

Figure 7

Temperature Sea Shipment Inside HOBO

Mean RH: 58.58% MAX: 78.62%
MIN: 51.37% Transit Time: 3.80days

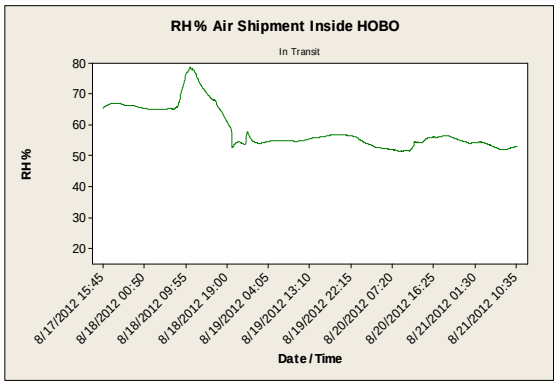

Figure 5

RH% Air Shipment Inside HOBO

MKT: 30.12°C MAX: 42.63°C
Min: 22.98°C Transit Time: 14.00days

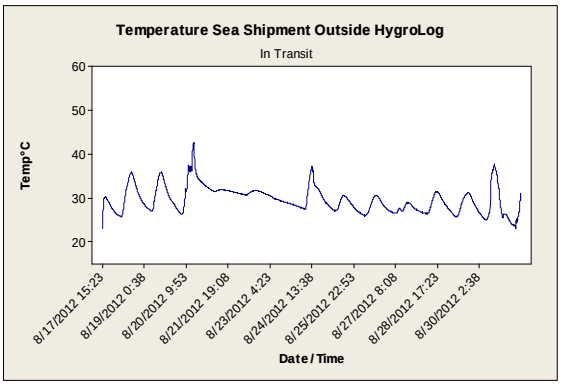

Figure 8

Temperature Sea Shipment Outside HygroLog

Mean RH: 53.79% MAX: 70.22%
MIN: 38.87% Transit Time: 3.80days

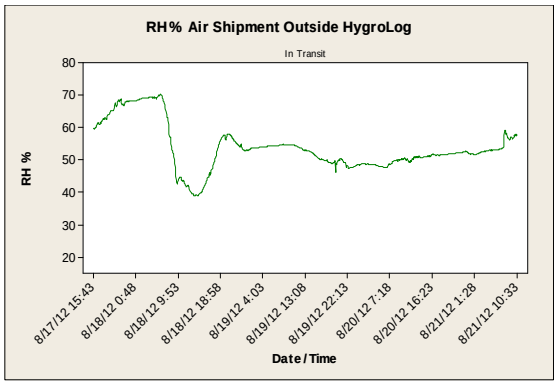

Figure 6

RH% Air Shipment Outside HygroLog

Mean RH: 63.09% MAX: 71.17%
MIN: 54.97% Transit Time: 14.00days

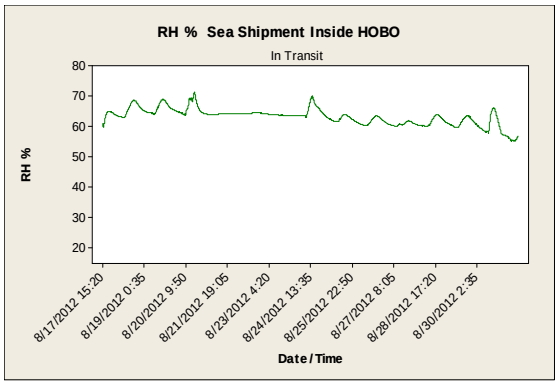

Figure 9

RH% Sea Shipment Inside HOBO

Mean RH: 60.63% MAX: 68.89%
MIN: 41.14% Transit Time: 14.00days

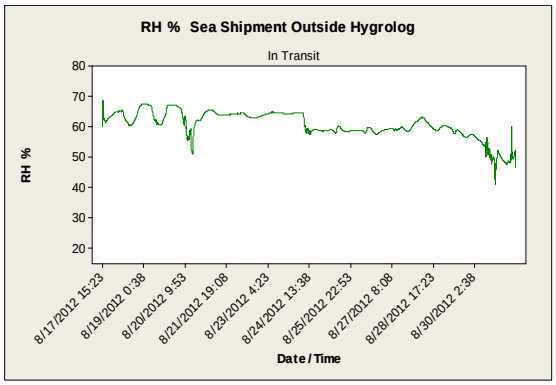

Figure 10
RH% Sea Shipment Outside HygroLog

CONCLUSIONS

The objectives of the shipping study were accomplished and provides documented evidence that the current shipping and transportation process via sea and air, for Y product from Puerto Rico to the receiving facility in US does not affect bulk quality attributes i.e., integrity, safety, efficacy, strength and purity as demonstrated with the execution of the project [2]. Mean Kinetic Temperature and average relative humidity data obtained during the bulk shipping study was within accelerated bulk stability conditions (40° C / 75 %RH for 1 month) [5]. Analytical data obtained as part of the bulk shipping study showed that the environmental conditions exposed during the bulk shipping study (e.g., Mean Kinetic temperature, average relative humidity and observed temperature and relative humidity spikes) did not impact quality attributes of the bulk drug product. The bulk shipping studies showed that the product was not impacted throughout the following range of observed Temperatures and Relative Humidity from inside and outside monitoring of drums:

- Range for Temperature / Relative Humidity (Air Shipment): (19.46 – 53.55 °C) / (38.87 – 78.62 RH %).
- Range for Temperature / Relative Humidity (Sea Shipment): (22.14 – 42.63 °C) / (41.14 – 71.17 RH %).

The analytical results were evaluated for the Y product as per material specification. The outcome of this evaluation was that transportation from Puerto Rico facility to the receiving facility has no impact in the critical quality attributes of the product with current bulk packaging configuration when exposed to the aforementioned environmental conditions.

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