Title: Evaluation Process Supporting Elimination of Defined Shipment Temperature Range for Solid Oral Dosage Forms					
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Prepared by:		Date:		Supersedes:	
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Evaluation Process Supporting Elimination of Defined Shipment Temperature Range for Solid Oral Dosage Forms

Introduction

Some GMP sites may be practicing to ship some oral dosage form products from manufacturing facilities to Distribution Centers under controlled (defined temperature range) temperature conditions. Given the characteristics and stability performance of many solid oral dosage form products, shipment under a defined temperature range is not necessary. This document provides the scientific and risk management assessment process to support the evaluation and, where appropriate, discontinuation of solid oral dosage form shipment under defined temperature range conditions, dependent upon the results of individual product analyses.

Assumptions

1. During summer months and in tropical climates, pharmaceutical products being shipped under ambient conditions have the potential to be exposed to elevated temperatures reaching an approximate maximum temperature of 50ºC (122ºF).

2. Review of central America to United States Distribution Centres shipment time indicates that the typical shipment time for these pharmaceutical products from manufacturing facilities to distribution centers is less than two weeks.

   The presented rationale may be applied to discontinue defined temperature range shipments for other shipping routes if the shipment time is known and falls within the assumptions of this model.

3. Since the maximum exposure to elevated temperatures occurs during day time hours (approximately 12 hours per day), for a two week shipment time the actual exposure to elevated temperatures is estimated to be a maximum of one week as a worst case scenario.

4. Applicability of this document is limited to solid oral dosage forms (e.g. tablets, hard gelatin capsules, powders, etc.). Given dosage form characteristics, shipment of other dosage forms (e.g. soft gelatin capsules, liquid products, etc.) should be performed under temperature conditions in accordance with product labeling.

$$k = Ae^{\frac{E_a}{RT}}$$

Where: E_a = Activation Energy
R = Universal gas constant (8.3144×10^{-3} kJ*mole^{-1}*degree^{-1})
T = Temperature in degrees Kelvin = 273.1+C°
A = Frequency factor (collision rate and steric factor)

How does the rate change when the temperature changes from 40°C to 50°C?
50°C = 273.1 + 50 = 323.1°K 40°C = 273.1 + 40 = 313.1°K

The ratio k_{50} / k_{40} estimates the rate change in the following equation:

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$$\frac{k_{50}}{k_{40}} = \frac{Ae^{-\frac{E_a}{R*323.1}}}{Ae^{-\frac{E_a}{R*313.1}}} = e^{\frac{E_a}{R}(1/313.1 - 1/323.1)} = e^{\frac{E_a}{R}*0.0000989}$$

Note: the ratio does not depend on A as it divides out in the math.

USP <1150> suggests using an Activation Energy of E_a = 83.144kJ*mole^{-1} for pharmaceutical products so E_a / R =10000 and

$$e^{10000*0.00009885075} = e^{0.9885075} = 2.687221$$

This calculation indicates that a product stored at 40°C will degrade 2.687221 times faster when stored at 50°C for the same time period.

$$k_{50} = k_{40} * 2.687221$$

A product that degrades *x* units in 3 months at 40°C will take only 3/2.687221=1.12 months (33 days) to degrade *x* units stored at 50°C.

$$Time_{50} = Time_{40} / 2.687221$$

This timeline of 1.12 months (33 days) exceeds the typical shipping time of product. Therefore, if acceptable 3 month stability data at 40°C exists, a temperature excursion of 50°C will have no negative impact on the product if exposed to the elevated temperature for less than 1.12 months (33 days). As indicated in Assumptions (3.) above, since the exposure to elevated temperatures would potentially occur only during day time hours (approximately 12 hours per day), the actual number of exposure days to achieve the equivalent of 1.12 months at 50°C would be approximately two months (66 days).

