Guidance Number: 87
The Arrhenius Equation

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

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

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.

$$Time_{50} = \frac{Time_{40}}{2.687221}$$

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).

<u>Therefore, if satisfactory 3 month 40°C/75%RH or 40°C stability data are available for a product, shipment of the product under ambient temperature conditions is supported.</u>

Additionally the impact of a product exposed to 50°C storage for 2 weeks, followed by storage at ambient temperature through various expiration periods was assessed with regard to mean kinetic temperature and summarized below:

Expiry	Weeks	25°C Storage	30°C Storage
		Mean Kinetic Temperature (MKT)	
18 months	78	27	31
24 months	104	27	31
30 months	130	27	31
36 months	156	26	31
48 months	208	26	31
60 months	260	26	30

Since a tolerance of +/- 2°C is acceptable for storage of drug product in stability chambers, changes in MKT greater than 2°C would indicate potential impact on stability performance over the expiry period. This analysis demonstrates that the impact of a 2 week 50°C excursion would not increase the MKT more than 2°C for expiration dates of at least 18 months; therefore, the impact on stability through expiry would be negligible.