Developing ISTA Cold Chain Environmental Standards

Industry approved testing profiles have not been developed for the Cold Chain transportation environment. This presentation will describe how to develop heat and cold testing profiles to meet your qualification needs.

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Abstract

Developing Amgen's Global Thermal Profiles

The Cold Chain transportation environment currently does not have industry approved testing profiles. This paper describes the process to develop a heat and cold testing profile to meet your qualification requirements.

Introduction

Amgen needed to develop ambient thermal profiles. It was necessary that these profiles represent global Amgen sites environmental temperatures. These profiles are required for use in qualifying insulated shippers that are to be used for the transportation of products worldwide.

Qualifying shippers to the thermal profiles allowed Amgen to use the same insulated shippers for shipping to different locations. The ambient profiles used in qualifying shippers covered the limits of heat and cold exposure that the package is expected to encounter during handling and transit. The two profiles, one for heat and the other for cold, were developed and compared with the mean kinetic temperature (MKT) of the two profiles.

The MKT is a method of expressing the overall effect of temperature during the storage or transit of pharmaceutical products. The MKT incorporates the nonlinear dependency of temperature upon a chemical reaction rate, as described by the Arrhenius equation. Sensitivity to temperature of a reaction is incorporated into the MKT.

Mean-kinetic temperature is expressed using the formula:

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

T_k mean kinetic temperature (°C)

ΔH heat of activation, 83.144 KJ/mol

R universal gas constant, 8.3145E-03 KJ/mol-degree

n total number of temperatures recorded per temperature recording device

T_n temperature recorded during period n (°C)

For the Amgen domestic profiles, distribution centers shipped corrugated non-insulated containers containing a temperature-recording device to various Amgen wholesalers representing a cross-section of the United States. The non-insulated corrugated shippers represented temperatures experienced by the outside of the polyurethane insulation. The carrier, United Parcel Service was used for all shipments. Shipments were sent using two-day air service. Upon arrival to their destination, the shipments were then returned to their origin where the recorded temperature data were downloaded into an Excel spread sheet format and analyzed. In order to develop a 72-hour profile using two-day air service, shipments were sent out on Thursdays and Fridays and the first 72-hours of transit data were used.

A seventy-two hour profile was desired for commercial shipment thermal profiles to include and additional twenty-four buffer to the two-day service. This provides support for situations in which product is delivered late. The Global profiles were developed based on two sets of Amgen domestic shipping data (summer and winter) and historical global data obtained from the National Aeronautics and Space Administration (NASA).

Results

Figure 1: Amgen Heat Profile

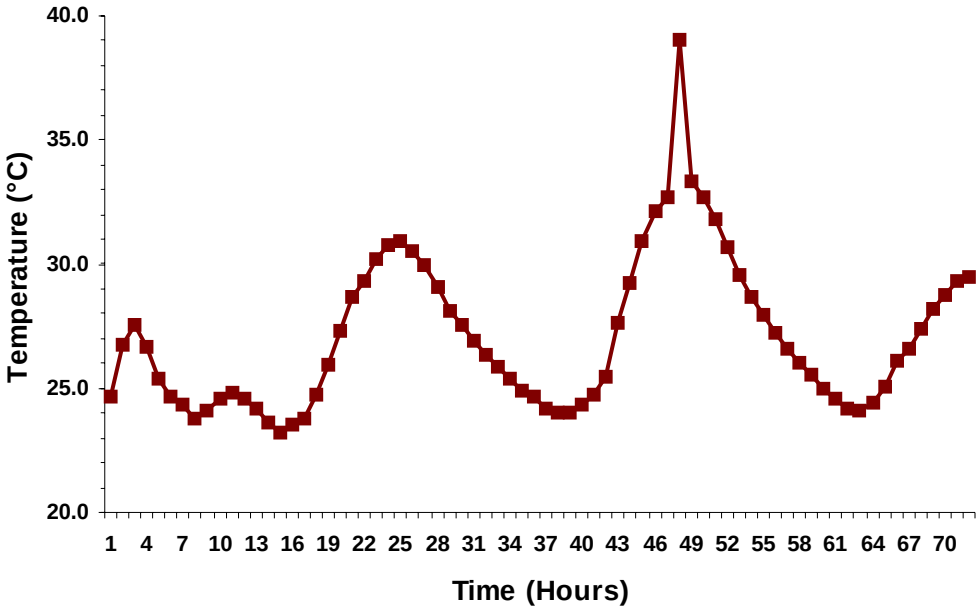


Figure 2: Heat Scatter Plot

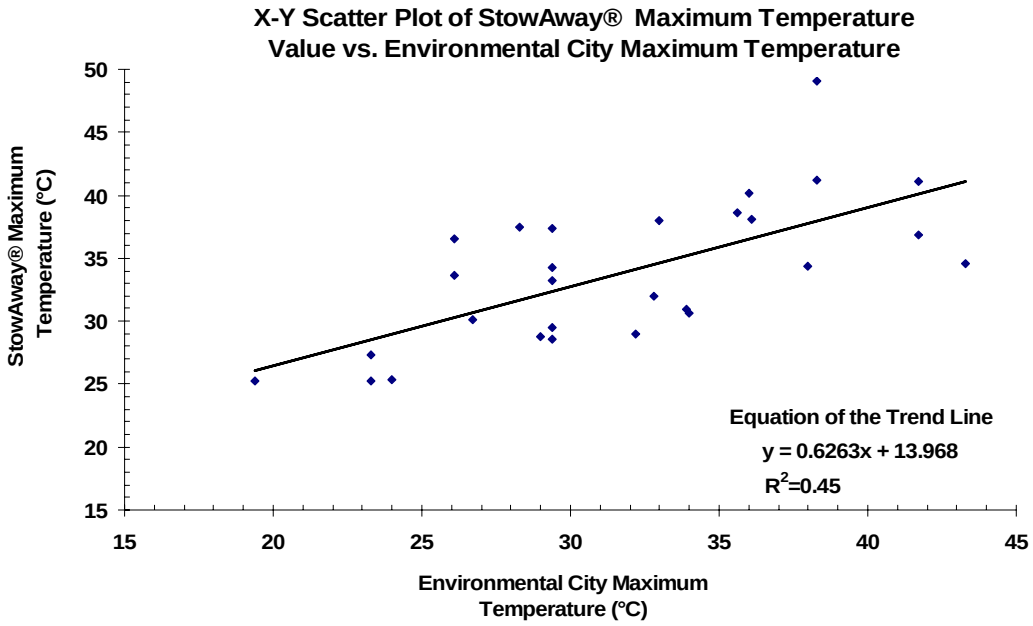


Figure 3: Amgen Global Transportation Heat Qualification Profile 144-Hours

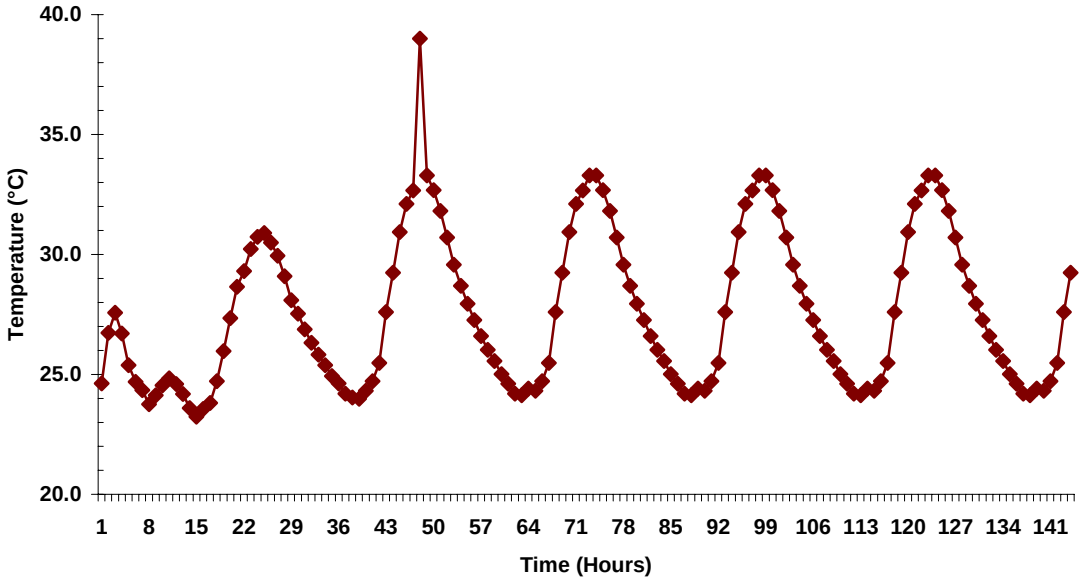


Figure 4: Amgen Global Transportation Cold Qualification Profile

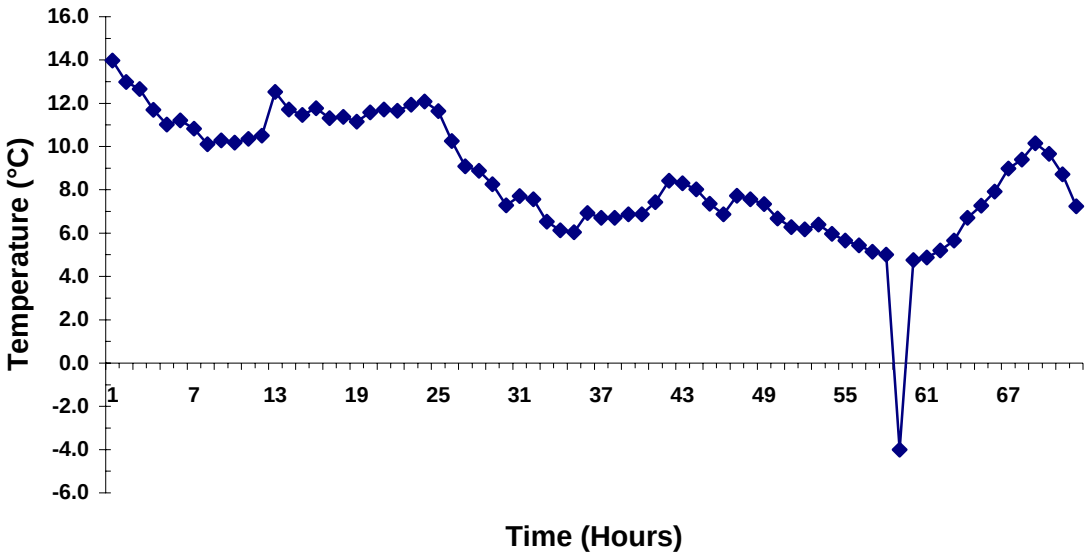


Figure 5: Cold Scatter Plot

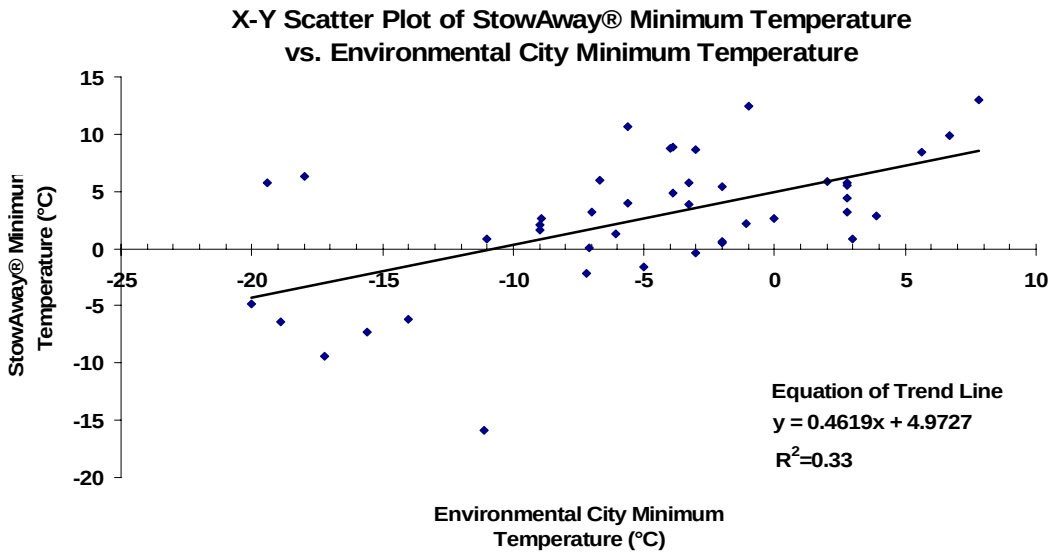
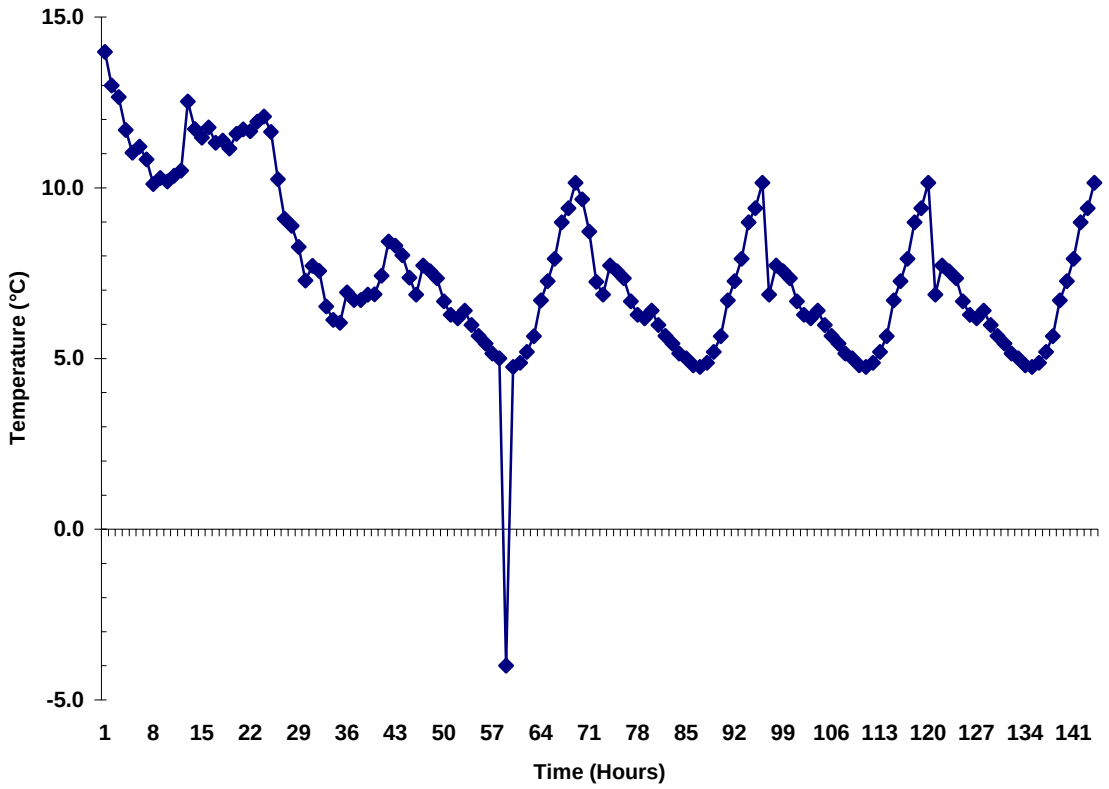


Figure 6: Amgen Global Transportation Cold Qualification Profile -144 Hours



Discussion

Heat Profile

The shape of the Amgen heat profile (Figure 1) represents the dynamics of environmental heating and cooling for the first 72 hours of shipments. The figure is based on actual data collected from Amgen distribution sites to distributors located across the United States

To show a relation between the continental United States and global temperatures a correlation between environmental temperatures and maximum internal temperature of the corrugated shipper was made. Using the Amgen shipment tracking records, the location/city with the maximum temperature was determined. Weather Underground (http://wunderground.com/) weather data from corresponding cities where the maximum StowAway® XTI Internal/External Temperature logger readings occurred were used to determine the maximum temperature of the cities on that specific date.

A graphic comparison of the NASA environmental and the interior temperature is best reflected in an X-Y Scatter Plot (Figure2: *X-Y Scatter Plot of StowAway® Maximum Temperature Values vs. Environmental City Maximum Temperatures*). A linear regression is shown on the graph. The equation of the trend line is y=0.6263x+13.968. This indicates the line of best fit has a slope of 0.6263 and a Y-intercept of 13.968. The correlation coefficient (R^2) was 0.45. Although the correlation coefficient is 0.45, there was no statistically significant lack of fit based on the repeated values of environmental city maximums. Therefore a simple linear equation is used to describe the relationship between the StowAway® maximum temperature and the environmental city maximum temperatures.

For the global heat profile, the maximum average monthly temperature of the global city sites was 35.9°C. This occurred in Phoenix, Arizona during the month of July in 1989. At 35.9°C, the internal shipper temperature is calculated to be:

$$Y=0.6263x + 13.968$$

$$Y = 0.6263(35.9) + 13.968$$

$$Y = 36.5°C$$

This indicates that when the environment is 35.9°C, the internal environment of the box is estimated to be 36.5°C. To increase the predicted confidence of this value, a statistical confidence limit of 95% was calculated and determined have an upper control limit of 38.5°C (Attachment 2B: *95% Confidence Interval Around the Regression Line of Maximum Temperature Values*). 38.5°C represents with 95% confidence the predicted temperature at which the shipper will experience when subjected to an environmental temperature of 35.9°. The current Amgen Summer profile consists of a maximum temperature of 33.3°C. To include the maximum monthly average temperature experienced in Phoenix, the maximum value of the heat profile is shifted to 39.0°C. This profile exceeds the maximum International Amgen distribution city average temperature (35.9). The *Amgen Transportation Heat Qualification Profile* (Figure 1) will encompass globally the maximum average environmental temperatures that the interior of Amgen shippers will experience.

The Amgen Transportation Heat Qualification Profile represents temperature changes experienced over a 72-hour period. Each 24-hour period represents day (warm) and night (cool). The maximum temperature reached is 39.0°C and the minimum temperature is 23.2°C. The 24-hour period of time representing the greatest temperature change occurs between hours 40 and 64 of the observed data. This change in temperature also represents the period of time, which the shipper experiences the greatest thermal challenge during qualification and is least influenced by the warehouse temperature, encountered at time zero. The last 8-hours of the profile are substituted with hours 40-47 in order to increase the rate of heating and the challenge to the insulated shipper.

To extend testing beyond 72-hours, continue repeating the 24-hour segment consisting of hours 40 to 64 excluding the temperature spike at hour 48, to the Amgen Global Transportation 72-hour Heat Qualification Profile beginning with hour 65 as illustrated in Figure 3.

Cold Profile

The shape of the Amgen Cold thermal profile (Figure 4) represents the dynamics of environmental heating and cooling for the first 72 hours of shipments. Figure 4 represents actual data collected from Amgen distribution sites to distributors located across the United States. The above thermal profile was then correlated against NASA environmental data to be sure that it represented global low temperatures.

To show a relationship between the continental United States and global temperatures a correlation between the environmental minimum average temperature and minimum internal temperature of the corrugated shipper was made. This correlation represents the minimum temperatures experienced during shipments from both Thousand Oaks and Louisville to the coldest winter locations of Massachusetts, Michigan, and Minnesota. Using the Amgen shipment tracking records, the location/city of the temperature minimum was determined. NASA weather data from the corresponding cities where the minimum StowAway® XTI Internal/External Temperature logger readings occurred were used to determine the minimum temperature of the cities on that specific date. The data was then analyzed in a similar manner to the heat profile data.

A graphic comparison of the NASA environmental and the interior temperature is best reflected in an X-Y Scatter Plot, (Figure 5, *X-Y Scatter Plot of StowAway® Minimum Temperature Values vs. Environmental City Minimum Temperatures*). A linear regression is shown on the graph. The

equation of the trend line is y=0.4619x+ 4.9727. This indicates the line of best fit has a slope of 0.4619 and a Y-intercept of 4.9727.

The correlation coefficient (R^2) is 0.33. There was not a statistically significant lack of fit based on the repeated X-values (environmental city minimums). A test for the curvature (X^2 term) failed to add any statistical value. Therefore, a simple linear equation is used to describe the relationship between the StowAway® minimum temperatures and the environmental city minimum temperatures.

For the global cold profile, the minimum average monthly temperature of the global city sites was –12.6°C. At –12.6°C, the internal shipper temperature is calculated to be:

$$Y = 0.4619x + 4.9727$$
$$Y = 0.4619(-12.6) + 4.9727$$
$$Y = -0.85°C$$

This indicates that when the environment is –12.6°C, the internal environment of the box is estimated to be –0.85°C. To increase the predicted confidence of this value, a statistical confidence limit of 95% was calculated and determined to have a lower control limit of –3.0°C. The temperature 3.0°C represents with 95% confidence the predicted temperature at which the shipper will experience when subjected to an outside temperature of –12.6°C.

The Amgen Global Cold 72-Hour Qualification Profile (Figure 4) encompasses globally the minimum average environmental temperatures that the interior of the shippers will experience. The Amgen Transportation Cold Qualification Profile represents temperature changes experienced over a 72-hour period. Each 24-hour period represents day (warm) and night (cool). The maximum temperature anticipated is 14.0°C, and the minimum temperature is –4.0°C. The 24-hour period of time representing the greatest temperature change occurs between hours 46 and 69 of the observed data. This change in temperature also represents the period of time in which the shipper experiences the greatest thermal challenge during qualification and is least influenced by the warehouse temperature.

To extend testing beyond 72-hours, continue repeating the 24-hour segment consisting of hours 46 to 69, excluding the temperature dip at hour 59, to the Amgen Global Transportation 72-hour Cold Qualification Profile beginning with hour 72 as illustrated in Figure 6.

CONCLUSION

The Amgen Global Transportation Heat and Cold profiles represent temperatures globally and shall be used for qualification of transportation packaging configurations.

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