The correct use of Mean Kinetic Temperature in GxP environments

Regulatory bodies and stakeholders in drug manufacturing and distribution have long been working together to create standards for temperature monitoring that will ensure the quality of drugs, devices and biotechnology. Over the last 15 years, the mean kinetic temperature (MKT) value has been identified as a potential tool for evaluating the impact of temperature on product quality. Recently the calculation has come to be frequently misapplied in GxP-regulated industry. Originally the MKT was proposed to guide stability studies, but it’s now often used for evaluating temperature excursions as part of Good Distribution Practice. There is currently no consensus on how MKT should be applied. In this article we will describe the origins of the value in GxP applications, how to perform the calculation, and give basic recommendations for its appropriate use.

Background

A definition from the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) defines MKT as:

“A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation. When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (J. Pharm. Sci., 60:927-929, 1971) can be used.” – ICH Q1A (R2) “Stability Testing of New Drug Substances & Products”

This document Q1A (R2) is one of the most commonly used and cited. It cites a 1971 paper from J. D. Haynes in The Journal of Pharmaceutical Sciences, which addressed the fact that climate-based temperature variation in uncontrolled pharmaceutical storage makes it difficult to select a single temperature for use in product expiry testing. Haynes sought to address this variation by calculating a ‘Virtual Temperature’ for use in expiry testing that would account for the expected temperature variability in a given region. Haynes’s equation for ‘Virtual Temperature’ is the same equation we know today as the calculation for MKT. Based on the Arrhenius equation, this calculation describes the temperature dependence of simple chemical reaction rates at ambient temperatures, wherein the rate of reaction generally doubles with every 10 degrees Celsius increase in temperature.

Essentially, mean kinetic temperature is a weighted non-linear average that shows the effects of temperature variations over time. It’s a useful value to know in several applications, for example when
planning long-term stability study temperatures. However, the MKT is different than other weighted average calculations because it takes into account the non-linear effect of temperature excursions.

In a 2001 paper, J. Taylor of the Medicines Control Agency (MCA) presented a different application for MKT. Taylor argued that it could be used to evaluate temperature excursions in product storage. This was a landmark change in the application of MKT, providing industry with a tool to better understand the quality impact of temperature excursions. Taylor’s new MKT application was widely accepted. It was a timely concept, especially in the light of the regulatory challenges faced within Good Distribution Practices. It should be noted that Taylor recommended caution in using MKT to evaluate temperature excursions. Although the MKT value can provide data on the total amount of product deterioration for a period of time that is equivalent to the incremental deterioration that would occur in separate excursions, the calculation is never to be used as a substitution for good environmental control and a detailed, study-based understanding of thermal properties in a given area.

Where and when to use MKT

We recommend using MKT for relatively stable, controlled room temperature environments during storage applications. We do not recommend the MKT calculation for the following environments or applications:

- Incubators
- Stability chambers
- Refrigerated or cold storage applications
- Long-term storage

A weighted, but non-linear average over time is best used when short excursions are less likely to cause serious harm (as in CRT) and over less time. The calculation makes sense in storage and distribution applications, especially where there can be fluctuations – either because of the climatic zone, or the season.

### Table 1: Basic Rules for Controlled Room Temperature

- Products marked with a CRT label should be stored at thermostatically controlled temperature at 20 – 25°C (77°F) and a mean kinetic temperature (MKT) calculated to be not more than 25°C with excursions permitted to 15 – 30°C (59 – 86°F).
- Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F). However, such exposure should be minimised.

### Understanding the calculation

The easiest and the most meaningful way to get an MKT value is by letting your monitoring software do the work for you. It is of course possible to do the calculation yourself, but remember that you need an extensive amount of data and a calculation tool (e.g. Microsoft Excel sheets). Additionally, any tool used for calculation of MKT for use in GMP decision-making would require validation.

The values used in the MKT formula are shown in the Equation Key. It should be noted that $\Delta H$, the activation energy, describes the reaction rate for the degradation of the active ingredients in a drug. A default value of 83.144 kJ/mol is typically used because it is a good approximation for most pharmaceutical compounds. Furthermore, it simplifies the math as it is numerically similar to the universal gas constant. Please note that it is possible to use a different $\Delta H$ value that is specific to a given product if the information is available.

### Table 2: Equation Key

| $\Delta H$ | the heat of activation, which equals 83.144 kJ per mol (default value; unless more accurate information is available from experimental studies) |
| $R$ | universal gas constant, which equals 8.3144 x 10^-3 kJ per degree per mol |
| $T_1$ | the (average) temperature, in degrees Kelvin, during the first time point |
| $T_2$ | the (average) temperature, in degrees Kelvin, during the second time point |
| $T_n$ | the (average) temperature, in degrees Kelvin, during the nth measured time point; n being the amount of the measured time points |
| $T_k$ | Result in degrees Kelvin. You’ll receive the final result MKT (in degree Celsius) by doing simple subtraction (TK – 273.15°K) |

In summary, we can make six basic recommendations for using mean kinetic temperature:

- MKT should not be used to compensate for temperature excursions in any application.
- When using MKT, ensure you have an adequate number of samples (time/temperature). MKT should not be used in areas where temperature is not well controlled.
- Use MKT only if the storage temperature specified on the label of the product does not exceed 25°C.
- MKT should not be used for products that require controlled low temperatures.
- Regardless of whether you use the MKT calculation or not, all temperature excursions should be investigated.

Mean kinetic temperature and its use in distribution and other GxP-regulated applications will likely continue to evolve as guidance, regulations, and technologies progress.

### References