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Application Note

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Mean Kinetic Temperature in GxP Environments

Mean kinetic temperature (MKT) was first developed for and applied to controlled room temperature (CRT) storage in warehouses.

Mean Kinetic Temperature:
"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."

From *ICH Q1A (R2) "Stability Testing of New Drug Substances & Products"*

Regulatory bodies and stakeholder organizations in drug and device manufacturing and distribution have long been working toward creating standards for temperature monitoring that ensure the shelf life, quality, and safety of products. In the last 15 years of these ongoing efforts, mean kinetic temperature (MKT) has been identified as one of the potential tools available for evaluating the impact of temperature on product quality.

MKT can be a difficult tool to understand and apply properly. MKT was first proposed to guide stability studies and is now considered as a tool for evaluating temperature excursions in the dynamic arena of Good Distribution Practices. The math is difficult for most laypersons, and there is not a consensus on how MKT should be applied.

Regulatory Bodies and Definitions

The document most cited in GxP-regulated industries for the definition of mean kinetic temperature is the International Conference on Harmonization (ICH) guideline: "Stability Testing of New Drug Substances and Products Q1A(R2)." The definition from this guideline is shown above. The original purpose of the 1971 Haynes paper was to address the fact that climate-based temperature variation in uncontrolled pharmaceutical storage made it difficult to select a single temperature for use in product expiry testing. Simply put, changes in storage temperatures can affect the rate at which products degrade. Haynes sought to address this variation by calculating a "Virtual Temperature" for use in expiry testing that would consider the expected temperature variability in a given region. The equation he developed for "Virtual Temperature" is the same equation that is used today to calculate MKT. It is based on the Arrhenius equation, which describes the temperature dependence of simple chemical reaction rates at ambient temperatures where the rate of reaction generally doubles with every 10 degrees Celsius increase in temperature.

When establishing the temperatures for long-term stability testing of products to be stored at room temperature (RT) or controlled room temperature (CRT), the mean kinetic temperature in any part of the world can be derived from climatic data. The WHO divides the world into four climatic zones: temperate, subtropical, hot/dry, and hot/humid, based on drug stability research. Rules described in ICH Q1A(R2) are meant for climatic zones I-II (USA, EU, and Japan).

The description for stability testing conditions in countries located in Climatic Zones III (hot and dry) and IV (hot and humid) can be found in ICH Q1F explanatory note and in the WHO technical report "Annex 2: Stability testing of active pharmaceutical ingredients and finished pharmaceutical products."

In practice, products stored at controlled room temperature are often tested for long-term stability in simulated laboratory conditions of 25 or even 30 degrees (at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ±5% RH) for dating purposes in climatic zones I-II, without using the exact calculated MKT value for a particular location. These temperatures are recommended by WHO in climatic zones I-II and (compared to the Haynes article) are probably high. They are an example of the worst-case scenario ideology often seen in the pharmaceutical and biotech industries. (For recommended long-term testing conditions all over the world, see the WHO Technical Report Series No. 953, 2009, Annex 2, Appendix 1 "Long-term stability testing conditions as identified by WHO Member States.")

For another regulatory source that defines mean kinetic temperature, refer also to the FDA's draft document: "Guidance for Industry, Stability Testing of Drug Substances and Drug Products." This draft gives a much briefer definition: "Mean Kinetic Temperature (MKT) is defined as the isothermal temperature that corresponds to the kinetic effects of a time-temperature distribution."

The U. S. Pharmacopeia (USP 43 Chapter <1160>, "Pharmaceutical Calculations in Pharmacy Practice") definition: "MKT is a single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures."

In short, MKT is a weighted non-linear average that shows the effects of temperature variations over time.

Mean kinetic temperature is the value used when planning long-term stability study temperatures. The value includes the annual variations, e.g., lower and higher temperatures during winter and summer seasons. Thus, storage at a continuous temperature of 25°C during a real-time stability study includes the actual temperature exposure likely to be encountered under ambient conditions throughout Europe, North American, and Japan, including real-time excursions from 25°C. However, MKT is different than other weighted average calculations because it accounts for the non-linear effect of temperature excursions.

The FDA and European Commission regard the calculation as a tool to help determine storage conditions, especially for shipping and storage in specific climatic zones. (See also the European Medicines Agency document from the Committee for Human Medicinal Products (CHMP) "Guideline on Declaration of Storage Conditions" 2007.)

Mean kinetic temperature may have uses beyond stability testing. In 2001, in a paper by J. Taylor of the Medicine Controls Agency, a different application for MKT was presented. Taylor argued that MKT could be applied to evaluate temperature excursions in product storage. This was a landmark change in the application of MKT, providing industry with a tool to evaluate the 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 in Good Distribution Practices. It should be noted that Taylor recommended caution in the application of MKT to evaluate temperature excursions.

The MKT value is supposed to encompass the total amount of product deterioration for a period that is equivalent to the incremental deterioration that would occur in separate excursions. However, the calculation is never to be used as a substitution for control and understanding of a controlled environment. Any temperature excursions must be rigorously investigated. An MKT value does not negate investigative responsibility because a short-term spike can indicate a larger problem, or a problem that may worsen. Root causes, as well as precise time and temperature data, must be documented and preventive actions then incorporated into a CAPA (corrective actions, preventive actions) management plan.

When & Where to Use Mean Kinetic Temperature

Because Vaisala's Continuous Monitoring System software viewLinc calculates MKT, we are often asked how to apply the calculation. MKT was first developed and applied to ambient storage in warehouses, and our recommendations are consistent with this application. We recommend using it for relatively stable, controlled room temperature environments during storage applications. MKT can be used for refrigerated applications if the typical degradation pathway is a chemical breakdown, rather than the result of spoilage. We do not recommend the MKT calculation for incubators and stability chambers, which are well controlled environments and not used for the storage of finished products. We do not recommend MKT for cold storage applications, as the degradation resulting from phase changes are not well described by the Arrhenius equation.

Nor is MKT ideal for long-term storage for the obvious reason that in any average over time, an increase in data points will eliminate spikes, such as a slowly climbing temperatures that may indicate an equipment breakdown. 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.

It is not internationally agreed as to whether MKT is suitable for use in evaluating excursions during transportation and shipping. For instance, the MHRA states that if the wholesale authorization holder can provide the marketing authorization holder with details of MKT, including the times and extent of any temperature deviations, this information may assist the marketing authorization holder in formulating advice to the wholesale authorization holder. This clearly indicates that the MHRA supports the use of MKT in transportation.

In addition, USP Chapter 1079, includes MKT among the tools available to address short-term temperature deviations during transportation.

In contrast, the German ZLG (Zentralstelle der Lander fur Gesundheitsschutz bei Arzneimitteln und Medizinprodukten/Central Authority of the German Federal Lander for Health Protection Regarding Medicinal Products and Medical Devices) states that the mean kinetic temperature is not appropriate for use in a transportation risk assessment. Again, this is because the value does not account for effects that may lead to irreversible quality defects, even when certain temperature limits established during stability studies are exceeded only for a short time. The MKT value also does not account for finer points such as the possible formation of fissures in glass ampoules and injection bottles at temperatures near freezing point.

Furthermore, calculation of MKT requires that the temperature profiles of all previous transports are known, but usually these data are not available.

The British Medicines Authority MHRA gives the following instructions: "MKT should not be used to compensate for poor temperature control of storage facilities. It may be applied in situations where control is relatively good, but where occasional excursions may be encountered."

J. Taylor.
"Recommendations on the Control and Monitoring of Storage and Transportation Temperatures of Medicinal Products,"
The Pharmaceutical Journal
(vol 267) July 2001

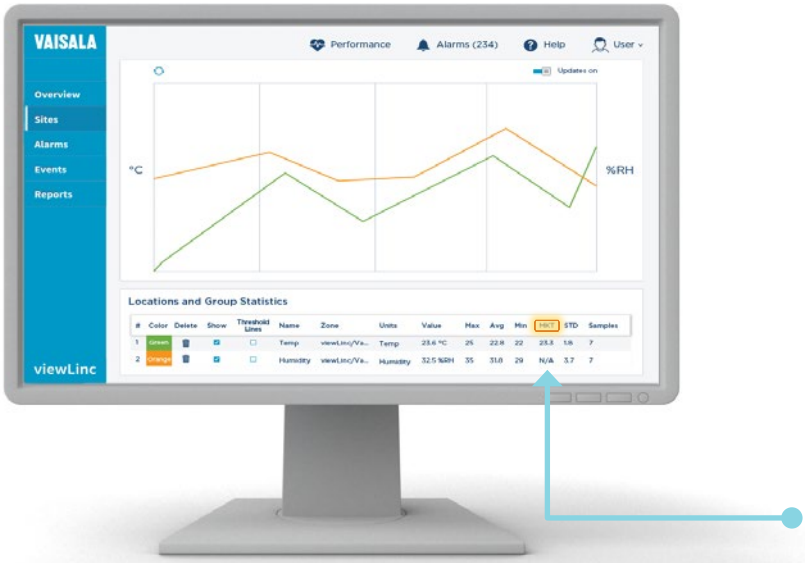
Ways to Calculate MKT

In its draft article for manufacturers, re-packagers, and warehouses, the FDA recommends inserting all data points into the MKT equation directly. A minimum of weekly high and low readings is recommended, and more rigorous approximations using daily highs and lows, or even more frequent temperature readings, are also described. When calculating a yearly MKT, a minimum of 104 weekly high and low readings would be used. The yearly MKT should be calculated from the monthly MKT calculations. The FDA recognizes that, when the yearly MKT of a facility begins to exceed 25˚C, it may not necessarily have an impact on products that have been stored for less than one year at the time. Rather, this value should be taken as a warning that the facility may not be under adequate control.

The USP provides some additional guidance in Chapter 1079 for calculating MKT for temperature excursions. For a CRT environment, a 30-day period is recommended, or the average time that a product is in the holder's possession. For refrigerated environments, this time drops to only 24 hours. If MKT is used to evaluate temperature excursions, it should only be for isolated short-term events that are not recurring. A storage or transportation system that has repeated excursions should be considered out of control.

It may be worth noting that many companies are moving away from using the term CRT in their operating procedures and documents. Many instead use a specific temperature range.

We recommend that control specifications be unambiguous and not subject to interpretation. It may be that CRT will fall into disuse in quality documents and standard operating procedures soon. EMEA guidelines support the same ideology. The use of terms such as `room temperature´ or `ambient conditions´ is unacceptable.



Avg	Min	MKT	STD
22.8	22	23.3	1.8
31.8	29	N/A	3.7

Figure 1: MKT is often calculated in continuous monitoring software.

The MHRA has stated: "It is not possible to obtain a meaningful MKT value from daily readings of simple max / min thermometers as temperature fluctuation is not a linear function. It is noted that some data loggers and building management systems are capable of recording multiple temperature readings over a time period and some offer the function of calculating the MKT over a given time period." The MHRA is clearly stating that continuous monitoring data can provide a more meaningful MKT value.

Regulations evolve with technology and like many monitoring systems, Vaisala's software viewLinc automatically calculates MKT, using every historical data sample. Simply select the timespan you are interested in and the MKT values will appear in the software window automatically. (Figure 1). Please note that mean kinetic temperature values alone should not be used in decision-making when temperature excursions have occurred. It is repeatedly mentioned throughout regulatory documents that information about the excursion duration and extent is required, as well as an evaluation of potential effects of the temperature excursion on product quality.

The MKT Calculation

The easiest and the most meaningful way to get an MKT value is by letting the data loggers and software do the work for you. It is possible to do the calculation yourself, but remember that you need an extensive amount of data and a calculation tool (e.g., Excel sheets). Otherwise, the calculation can easily be overwhelming. Furthermore, any tool used for calculating MKT for use in GMP decision making requires validation.

The equation is:

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

The values used in the MKT formula are shown at right in the Equation Key. It should be noted that ΔH, 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 as it is a good approximation for most pharmaceutical compounds. The default value simplifies the math because it is numerically similar to the universal gas constant. Please note that it is possible to use a different ΔH value that is specific to a given product if that information is available.

If you want to see some simplified examples how to calculate the MKT, please check USP 43 Chapter <1160> "Pharmaceutical Calculations in Pharmacy Practice." Bear in mind that MHRA doesn't support these simplified calculations, nor does the FDA.

Equation Key

- **ΔH** = 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 subtraction (T_K – 273.15°K)

Conclusion

To summarize, we can make six basic recommendations for using mean kinetic temperature:

1. MKT should not be used to compensate for temperature excursions in any application.
2. When using MKT, ensure you have an adequate number of samples (time/temperature). The more samples included in the equation, the better the MKT calculation.
3. MKT should not be used in areas where temperature is not well controlled.
4. Use MKT only if the storage temperature specified on the label of the product does not exceed 25˚C.
5. MKT should not be used for products that require temperatures below freezing.
6. Regardless of whether you use the MKT calculation or not, all temperature excursions should be investigated.

We hope that this exploration of the history and application of MKT is useful. This topic, and its applications in distribution, will likely continue to evolve as guidance, regulations, and technologies progress.

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