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The Use of Mean Kinetic Temperature and the Need of Allowable Excursion Limits for Climatic Zone IVb

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ABSTRACT

There is a growing concern about the proper storage and transportation of finished drug products, because storing and transporting products outside of their storage specification can potentially impact product quality, efficacy, and safety. However, although every effort should be made to keep the drug product within the temperature range indicated on the packaging, temperature excursions can occur. Once it occurs, the impact should be assessed. Mean kinetic temperature (MKT) is a single calculated temperature at which the total amount of degradation during a given period is equal to the sum of the individual degradations that would occur at various temperatures. However, MKT alone is not enough to assess the impact of a temperature excursion. It is necessary, in addition to MKT, to know the following: the time period of the temperature excursion, the actual excursion temperature(s), if there was a temperature excursion above 40°, and the time frame used to calculate MKT. Allowable excursion limits are essential to answering those questions and assessing the severity of excursions in a risk-based approach. MKT temperature excursion limits in *Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products* ⟨1079.2⟩ are specific for products stored at controlled room temperature (20°–25°) and at controlled cool temperature (2°–8°). As currently written, the chapter does not consider product storage between 15° and 30°, which is generally the storage and transportation range for drug products in climatic zone IVb countries. Establishing allowable temperature excursion limits for climatic zone IVb is particularly important at this moment not only to assess the impact of an excursion to the product during distribution, but also to establish an acceptance criteria for lane temperature profiling studies (lane temperature mapping). Setting MKT excursion limits for the storage and transportation of drug products in climatic zone IVb will be an important resource globally, so the aim of this *Stimuli* article is to present the case for updating ⟨1079.2⟩ to address MKT for climatic zone IVb.

INTRODUCTION

In March 2022, the US Pharmacopeia (USP) Latin America (LATAM), in partnership with Sindusfarma (Pharmaceutical Products Industry Companies Union) and the Brazilian Academy of Pharmaceutical Sciences—two important stakeholders in Brazil, organized a workshop on good distribution practices of finished drug products (GDP). This event was an opportunity to share more about USP's resources related to GDP, including general chapter *Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products* ⟨1079⟩ and *Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products* ⟨1079.2⟩. The program also included presentations on the GDP regulatory framework in Brazil (ANVISA Resolution, RDC No. 430/2020), utilization of mean kinetic temperature (MKT) to evaluate temperature excursions in different regions of Brazil and the methodology and results of a lane qualification pilot study executed to be in compliance with ANVISA GDP regulation.

There were over 800 workshop participants, including regulators, Brazilian trade associations (drug manufacturers, distributors, and transporters), and regulatory affairs professionals. Active discussion during the question-and-answer session led to insightful questions being posed as well as USP LATAM identifying gaps in MKT knowledge within Brazil and within USP's MKT standard. Some of the discrepancies identified included how temperature excursions are handled in Brazil, confusion around MKT use, how USP MKT excursion limits apply to the storage and transportation of drug product in climatic zone IVb, and the potential for updating the USP MKT standard to accommodate storage and transportation of drug products in climatic zone IVb.

In general chapters *Packaging and Storage Requirements* ⟨659⟩ and ⟨1079.2⟩, MKT temperature excursion limits are specific for products stored at controlled room temperature (CRT, 20°–25°) and at controlled cool temperature (2°–8°). As currently written, the chapters do not consider product storage between 15° and 30°, which is generally the storage and transportation range for drug products in climatic zone IVb countries.

In parallel, USP internal research identified the topic of temperature excursions and climatic zone IVb as an area where further USP guidance may be necessary and supported the Packaging and Distribution Expert Committee to look further into the topic. Because setting MKT excursion limits for the storage and transportation of drug products in climatic zone IVb will be an important resource globally, the aim of this *Stimuli* article is to outline the rationale for updating ⟨1079.2⟩ to address the use of MKT for climatic zone IVb and proposing excursion limits.

PHARMACEUTICAL SUPPLY CHAIN AND THE RISK OF TEMPERATURE EXCURSIONS

A holistic view of the pharmaceutical supply chain should be done to understand the risks related to temperature excursions, considering factors such as (*Figure 1*):

- The complexity of the supply chain with multiple supply chain partners
- Two key activities common to all supply chain partners: storage and transport
- The use of different modes of transport that allow the movement of product along the supply chain, from manufacturer to customer
- Global supply chains can have different local regulations and different climatic zones serving as complicating factors
- All supply chain partners have joint responsibility

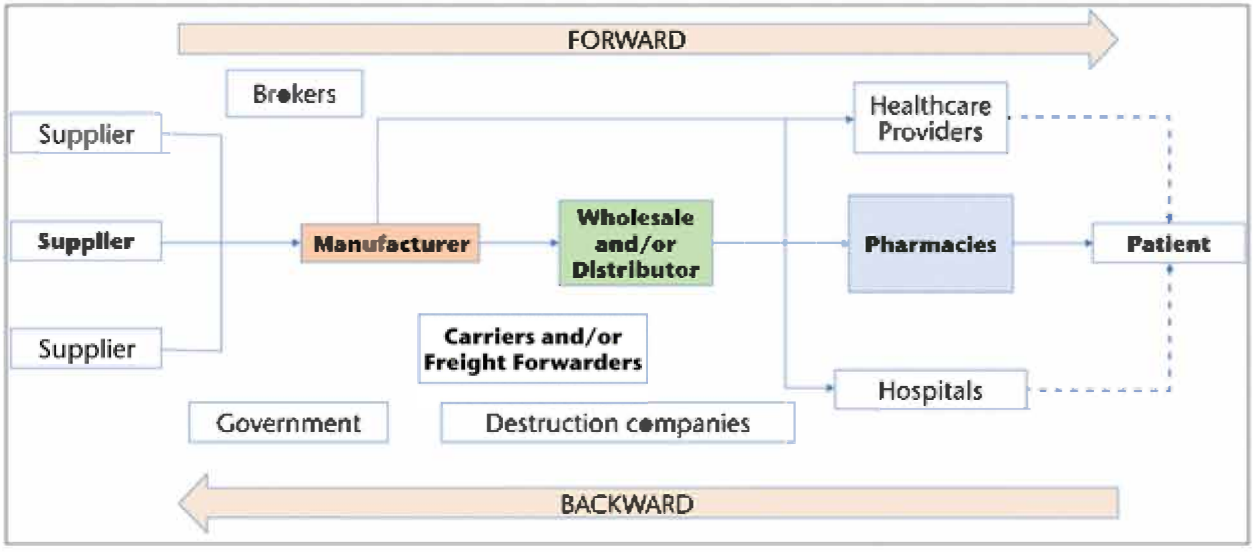

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Figure 1. Pharmaceutical supply chain.

To maintain the original quality of the product, every party involved in the storage and transportation of a finished product should have an in-depth understanding of the storage and transportation risks and have the appropriate mitigation strategies in place to control these risks.

Organizations should devote effort and resources to the transport, handling, and storage of drug products in such a way that reduces the risk of exposure to temperatures outside the labeled storage conditions, also known as temperature excursions. Although every effort should be made to keep the drug product within the temperature range indicated on the packaging, temperature excursions can occur. In climatic zone IVb, drug products whose stability studies were conducted to provide storage from 15° to 30° are often transported in nontemperature-controlled vehicles that can go through various temperature extremes during a journey or are stored and in-transit storage facilities that do not have thermostatic control of temperature. Even in stability chambers, where drug products stability studies are conducted with varying temperature and relative humidity, temperature excursions can occur. Not addressing stability chamber excursions is a frequent audit finding, as is evidenced by a sampling of Warning Letters from the FDA, as mentioned by Huynh-Ba and Latoz (2021).

Temperature excursions are a risk in today's pharmaceutical supply chain and when observed should be assessed, reduced, and communicated. The effect of an excursion can be a loss of assay, the increase of impurities, precipitation of drug, change in dissolution pattern, phase changes, etc. (Nirmal and Ajeya, 2017). These effects depend on product stability and the temperature and the duration of the excursion.

Without risk assessment, temperature excursions often result in considerable losses for public health programs operating in countries with limited resources. In order to assess the impact of a temperature excursion, consulting the manufacturer is the preferred approach. However, this can be challenging depending on data availability and the responsiveness of the drug product manufacturer (Jenkins et al., 2022). Thus, MKT can be a useful tool when stability data is not known by a downstream supply chain partner.

Chapter ⟨1079.2⟩ defines MKT as the single calculated temperature at which the total amount of degradation during a given period is equal to the sum of the individual degradations that would occur at various temperatures. It is a way of summarizing the exposure time history of a product with a single "effective" or "virtual" temperature. Thus, MKT integrates the time-temperature history by making assumptions about the kinetics of the chemical degradation of a product.

Basically, the Arrhenius equation demonstrates that a rate of reaction will increase exponentially with temperature, rather than linearly. Correspondingly, MKT is important to understand because it provides the effective isothermal temperature experienced by the product that accounts for the Arrhenius-based effect of temperature excursions during storage (Jenkins et al., 2022).

Although MKT is a valuable tool in helping to access a temperature excursion, it may not be appropriate in some situations. For example, in cases where a product is subject to phase change (suppositories, liquids, suspensions, emulsion, creams, etc.) and/or where clinical data indicate that temperature excursions can impact product quality and safety. Health Canada (2020) also noted biologics as a category of products for which MKT may not be suitable. If MKT cannot be used, stability and stress studies and freeze and thaw and high temperature cycling studies can be used to analyze the risk and justify the decision-making process to sell or dispose the product. Thus, when MKT is not appropriate for assessing a temperature excursion, this point should be communicated to supply chain partners.

In using MKT to evaluate a temperature excursion, it should not be abused. MKT alone is not enough to assess the impact of a temperature excursion and it is necessary to also know the following:

- How long was the temperature excursion?
- What were the excursion temperature(s)?
- Was there a temperature excursion above 40°?

- What time frame was used to calculate MKT?

SUGGESTION FOR ALLOWABLE EXCURSION LIMITS FOR NONCONTROLLED ROOM TEMPERATURE IN CLIMATE ZONE IVB BY ANALOGY TO CRT

The rationale and foundation for the potential excursion limits for climatic zone IVb was based on the current excursion limits for CRT. The current limits for CRT and suggested limits for storage from 15° to 30° (RT in climatic zone IVb) is shown in *Table 1*.

Table 1

	Storage Range	MKT (NMT)	Time Period of MKT Calculation	Acceptable Excursion Range	Maximum Temperature (NMT)	Maximum Excursion Time (h)
CRT	20°–25°	25°	30 days or the time a product remains in the organization's possession	15°–20° and 25°–30°	Transient spikes 40°	24 h
RT[a] in Climatic Zone IVb	15°–30°	30°	30 days or the time a product remains in the organization's possession	30°–40°[b]	40°	24 h

[a] RT, room temperature.

[b] At room temperature in climatic zone IVb any excursion below 15°, even with MKT NMT 30° should be evaluated case by case.

The MKT limit for room temperature in climatic zone IVb should not be more than 30°, as this is the isothermal where the long term stability for this condition was established.

The time period used in calculating MKT should be for 30 days or the time a product remains in the organization's possession, as established in ⟨1079.2⟩. Because MKT is a calculation, the use of an extended period of time would bias the calculation by including a majority of temperature data points outside the excursion, thus presenting an inaccurate picture of the MKT and, consequently, the real impact of the excursion.

The maximum temperature excursion should be NMT 40°, as 40° is the standard ICH accelerated condition for room temperature drug products. If satisfactory stability data is available, temperature excursions beyond 40° could be accepted. Temperatures higher than 40° increase the likelihood for product degradation. The adverse impact of lower excursion temperatures has also been demonstrated, which can lead to loss of therapeutic effect or poor product quality. Precipitation of the drug product or the dislocation of the lattice positions are some examples of the adverse effects of low temperature excursion in some products (Nirmal and Ajeya, 2017). For this reason, temperature excursions below 15° should also be evaluated for impact, because the classical stability studies do not challenge products for low temperature exposure when developing product storage requirements at 15°–30°. Temperatures from 2° to 15° present a risk *only* for precipitation of very concentrated solutions. For all other drug products, such temperatures just slow down any degradation processes.

It is the assumption that a 24-h excursion within the acceptable excursion range would have negligible impact on the product. However, as stated previously, there are certain products that might have a narrow

tolerance for temperature excursions and in this situation, MKT should not be used to evaluate an excursion. The idea of a 24-h excursion range is supported by the following:

- ICH (2003) established that excursions in storage facilities for formal stability studies that exceed the defined tolerances for more than 24 h should be described in the study report and their effect assessed.
- The study of Jenkins et al. (2022) showed a shelf-life loss of 2 weeks for a solid dosage form that had a 24-month self life. The maximum storage temperature for the product was 30° and with a temperature excursion at 40° of 6 days, the impact was minimal.

The frequency of temperature excursions should be evaluated periodically by quality professionals. For cases where there are recurring observations of excursions from a particular facility or lane, a decision should be made (Nirmal and Ajeya, 2017) and a CAPA (corrective action and preventive action) opened to determine the process and measures to be taken, if any. A common problem that should be ruled out is failure by receiving staff to turn off temperature monitoring devices once a product has been stored and the device removed.

Establishing temperature excursion limits for climatic zone IVb is of particular importance at this moment, not only to assess excursions during distribution, but also to establish acceptance criterion for lane temperature profiling studies (lane temperature mapping) to select lanes and then perform the necessary qualifications.

CONCLUSION

The storage, handling, and transportation of a drug product must be kept under recommended storage conditions to maintain its quality, safety, and efficacy.

MKT cannot be used to normalize storage conditions situations that are out of control but can be a valuable tool to evaluate a temperature excursion. Thus, the use of MKT in evaluating a short term excursion (as defined in ⟨1079.2⟩) and the time frame used to calculate MKT as recommended by USP can allow for responsible management of excursion risk.

The temperature excursion limits for climatic zone IVb in this article that were suggested for updating ⟨1079.2⟩ can help supply chain stakeholders in the decision-making process as to whether to keep or discard a product after excursion. Products from public health programs operating in countries with limited resources will not be lost due to a lack of a standard to help evaluate the risk and the impact of a temperature excursion. Therefore, those limits will allow the stakeholders when performing lane temperature profiling studies to decide for which lanes the product should have a qualified passive or active protection. Therefore, these limits can also be applied for products distributed in climatic zones III and IVa, if the products were tested during long term stability at 30° and are stored at a room temperature of 15°–30°.

ADDITIONAL SOURCES OF INFORMATION

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