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4 December 2019

Dr. Desmond Hunt
U.S. Pharmacopeia
12601 Twinbrook Pkwy
Rockville MD 20852

Re: PF 45(5) Proposed Revisions to General Chapters <659> and <1079> and Proposed New General Chapter <1079.2>

Dear Dr. Hunt,

PDA appreciates the opportunity to provide input into USP's proposed revisions to General Chapters <659> Packaging and Storage Requirements and <1079> Good Storage and Distribution Practices for Drug Products, and proposed new General Chapter <1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products. We provide specific suggestions in the attached document.

While PDA appreciates that USP is attempting to limit the use of Mean Kinetic Temperature (MKT), we believe that the language USP uses in this revision is still too broad and may allow for the usage of MKT in circumstances in which it is not scientifically sound. While MKT can be a mathematically sound way of representing a time-averaged single number temperature exposure figure, the complexities of the data in drug and biologic distribution make accurate application significantly more complex than suggested.

Because MKT should be used only where it is scientifically supportable, PDA suggests eliminating the references to MKT from General Chapter <659> and instead insisting that all excursions be referred to the drug product manufacturer. Because the drug product manufacturer possesses all stability data for the product, the manufacturer can determine whether MKT is applicable in the specific circumstances. This approach will allow for more precise decisionmaking about product disposition. Such data-based assessments may even demonstrate the continued stability of the product over excursions that would not be permitted using the MKT caculation—an important consideration in a time of shortages of critical drugs. Because excursions should be limited due to modern active and passive transport systems, well controllable warehouses, and the increasing implementation of good distribution practices globally, this change should have only a modest impact.

This position is aligned with the conclusions reached by regulatory bodies. For instance, Ireland's Health Products Regulatory Authority states that "The [manufacturing authorization] holder should be consulted as to whether these excursions affect the thermal stability of the products in question and hence whether or not the use of MKT is applicable."[1] The German Federal Lander for Health Protection Regarding Medicinal Products and Medical Devices concludes that MKT is not appropriate for use in a transportation risk assessment.[2]

1. MKT can only be used where it is supported by stability studies

Any excursion investigation should be based in sound science. For many marketed products, stability studies as well as comprehensive storage and transport validation can

provide the scientific justification necessary to support disposition decisions. With this data, a manufacturer may be able to justify the use of MKT for its product. While PDA agrees that MKT may be suitable for many products manufactured to USP standards, PDA also feels strongly that, because of the wide range of products covered by USP monographs, it cannot be applied universally to all Controlled Room Temperature and Controlled Cold Temperature drugs.

Products of particular concern are cold chain products and vaccines. For these products, temperature excursions should not exceed the limits determined through stability studies and additional transportation stability studies (extreme temp studies and temp cycling studies) as defined in paragraph 3.4 of PDA Technical Report 39 *Stability testing to support distribution of new drugs products*. These additional studies have been requested by several authorities, including ANVISA.

Moreover, MKT does not fully account for the full range of conditions in distribution and warehousing.[3] For instance, MKT does not account for heat transfer occurring through conduction, convection, and radiation, and the chapters do not discuss the consideration and assessment of these types of heat transfer. In addition, the impact of temperature excursions will vary based on volume, with bulk ingredients in large volumes affected differently by the same temperature excursion than drug products for final distribution packed in single or multi-unit packages, in shippers, case packs and stacked on a pallet. Likewise, solid dosage forms may respond differently to environmental changes than liquid dosage forms, and syrups may respond different than water-like liquids. These scenarios demand specific application of data rather than a broad-brush application of MKT.

2. **MKT cannot be used for biological and vaccine products**

In general, PDA cannot support the use of MKT for biologicals and vaccines. MKT is based on an inappropriate theoretical hypothesis for biologicals and vaccine products, with significant drawbacks from the point of view of advanced kinetics. The assumptions behind MKT, including the assumption that the activation energy amounts to 83.144 $kJ \cdot mol^{-1}$, are often not appropriate for biological products, leading to incorrect evaluation of the aging extent.

More precise models than simple first-order kinetics are commonly required to well describe degradation rates in biological products. Among them, two-step kinetic models such as those developed and implemented for various types of vaccines[4-8] better mimic the complicated decomposition of the investigated samples. The use of two-step kinetic models led to accurate stability predictions of samples during shipments including temperature excursions.[8]

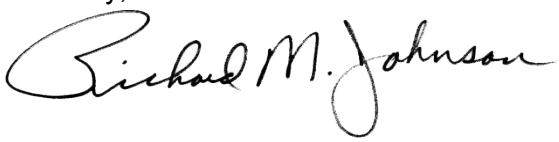
It has been demonstrated that simple models such as first-order kinetics used by the concept of MKT can induce significant errors in term of stability predictions.[4, 8-9] Only more precise models guarantee realistic estimations of the level of deterioration of products following temperature excursion.[8-9]

In practice, the application of concept of MKT can lead to incorrect conclusions for most biological products. The errors exist on both sides of the calculation: samples that are still good are rejected, and other samples are accepted despite the fact that they could be damaged.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality, and is an ANSI-accredited standards development organization. Our input has been prepared by a committee of experts in pharmaceutical stability and distribution on behalf of our Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me at johnson@pda.org.

Sincerely,



Richard Johnson
President and CEO

cc: Tina Morris, PDA; Ruth Miller, PDA

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[1] HPRA. Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances. 2017. https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/ia-g0011-guide-to-control-and-monitoring-of-storage-and-transportation-conditions-v2.pdf.

[2] http://nordiclifescience.org/vaisala/2017/11/01/mean-kinetic-temperature-gxp-environments/, accessed Oct. 29, 2019.

[3] We also note that MKT should only be used in environments that are thermostatically controlled. It should not be used when there is no control over the internal environment. MKT should not be used to justify regular excursions due to inadequate thermal control or poor operating procedures (e.g. load capacity of HVAC/refrigeration inadequate for the room or frequent excursions due to personnel mishandling of equipment). While USP makes these points in <1079.2>, PDA is concerned about the potential for misuse of MKT in any of these scenarios.

[4] D. Clénet, F. Imbert, P. Probeck, N. Rahman, S.F. Ausar. Advanced Kinetic Analysis as a Tool for Formulation Development and Prediction of Vaccine Stability. J. Pharm. Sci. 103:3055–3064, 2014, *doi: 10.1002/jps.24117*

[5] D. Clénet , V. Hourquet, B. Woinet, H. Ponceblanc, M. Vangelisti. A spray freeze dried micropellet based formulation proof-of-concept for a yellow fever vaccine candidate. Eur. J. Pharm. Biopharm., 142:334-343, 2019, *doi: https://doi.org/10.1016/j.ejpb.2019.07.008*

[6] D. Clénet, T. Vinit, D. Soulet, C. Maillet, F. Guinet-Morlot, A. Saulnier. Biophysical virus particle specific characterization to sharpen the definition of virus stability. Eur. J. Pharm. Biopharm., 132:62-69, 2018, *doi: https://doi.org/10.1016/j.ejpb.2018.08.006*

[7] B. Roduit, M. Hartmann, P. Folly, Alexandre Sarbach, Richard Baltensperger. Prediction of thermal stability of materials by modified kinetic and model selection approaches based on limited amount of experimental points. Thermochimica cta 579: 31–39, 201, 2014, *doi: 10.1016/j.tca.2014.01.005*

[8] D. Clénet. Accurate prediction of vaccine stability under real storage conditions and during temperature excursions. Eur. J. Pharm. Biopharm.: 125:76–84, 2018 *doi: 10.1016/j.ejpb.2018.01.005*

[9] B. Roduit, C.A. Luyet, M. Hartmann, P. Folly, A. Sarbach, A. Dejeaifve, R. Dobson, N. Schroeter, O. Vorlet, M. Dabros, R. Baltensperger. Continuous Monitoring of Shelf Lives of Materials by Application of Data Loggers with Implemented Kinetic Parameters. Molecules, 24(12), 2217, 2019, *doi: https://doi.org/10.3390/molecules24122217*

General Comments

General Comments	Rationale	Critical Comment? Y/N
As noted in our cover letter, we recommend removing all references to MKT in <659>, as this calculation cannot be universally applied. Because some drug product manufacturers might determine, based on their own stability data, that they may apply MKT to a specific product, USP might consider how to clearly present information about the optional use and application of MKT *by drug product manufacturers* in a single Information Chapter. We have not identified all of the necessary changes to General Chapters <1079> and <1079.2> to align with this approach.		

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
<659>	Controlled cold temperature: The temperature maintained thermostatically between 2° and 8° (36° and 46° F) that allows for an excursion experienced during storage or shipping. Mean kinetic temperature (MKT) may be used during an excursion provided: 1) the temperature is between 8° and 15° (46° and 59° F); 2) excursion time is NMT 24 h; and 3) calculated MKT is NMT 8° (46° F) with no excursions below 2° (36° F) or above 15° (59° F). These limits (time and temperature) and the calculated MKT must be documented. Additional controlled cold chain	Controlled cold temperature: The temperature maintained thermostatically between 2° and 8° (36° and 46° F), with excursions being acceptable only as determined and instructed by the drug product manufacturer and supported by stability data.	As discussed in our cover letter, the use of MKT should be limited to those circumstances in which it is supported by evidence. Only the manufacturer has this data; thus, all excursions should be assessed by the manufacturer. Alternatively, USP could consider defining CCT as "The temperature maintained thermostatically between 2° and 8°, with excursions as permitted," then including a definition of "excursion" in this chapter that describes the acceptable range of excursions. This revision also avoids another point of confusion in the proposed definition. In both the definition of	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	excursions may be permitted only if the drug product manufacturer so instructs and they are supported by stability data.		CCT and CRT, USP mentions "an excursion." It is not clear in the proposed definition whether USP intends to allow only one (and no more) excursion during the entire distribution cycle, or whether the product might experience an excursion within the MKT parameters at more than one stage of the supply chain. By eliminating the reference to MKT and instead requiring all excursions to be supported by stability data, USP avoids confusion about how to handle multiple excursions.	
<659>	Controlled room temperature: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F). MKT may be used during an excursion provided: 1) MKT does not exceed 25°; 2) excursion between 15° and 30° (59° and 86° F); 3) transient spikes are NMT 40°; and 4) excursion time is NMT 24 h. These limits (time and temperature) and the calculated MKT must be documented. Additional	Controlled room temperature: The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77° F), with excursions being acceptable only as determined and instructed by the drug product manufacturer and supported by stability data.	First, the definition of CCT and CRT should be aligned to the extent possible, to allow the reader to easily distinguish the differences. Second, in the definition of CRT as proposed, PDA found several points confusing. For instance, additional clarity would be required to address excursions from 30° to 39°. Is any temperature above 29° unacceptable? Or is the language about "transient spikes are NMT 40°," intended to cover these excursions? If USP were to retain that language, USP should clarify whether excursions between 30°	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
	excursions may be permitted only if the drug product manufacturer so instructs and they are supported by stability data.		and 39° are covered by that language, define "spike," and describe how it is different from an excursion. Is a spike an excursion that lasts only seconds or minutes (e.g., NMT 5 minutes, NMT 10 minutes)? Would an excursion of up to 24 hours be considered a spike if it reached 39°? In addition, if USP were to retain the references to MKT, USP might consider that MKT can be applied to two types of CRT excursions: 1) Excursions that stay between 15°-30°, which would require a review of MKT data in some form or fashion to ensure that MKT did not exceed 25°, and 2) Excursions that exceed 30° which would require the same MKT data review but also a review to ensure that transient spike did not exceed 40° range and lasted less than 24 hours.	
<1079> section 4.1.5	short-term excursions	~~short-term~~ Excursions	"Excursions" are defined in <659> without using the term "short-term," so those words are unnecessary here. If USP wishes to include the words "short-term," please consider defining what this	Y

Line No.	Current Text	Proposed Change	Rationale	Critical Comment? Y/N
			means, if different from the definitions in <659>.	
<1079> section 4.1.5	Each excursion should be documented and handled as a deviation. … Excursions out of temperature range defined by thermostability data or <659> should be addressed/corrected in order to prevent recurrence using a risk-based approach.	Each excursion should be documented and handled as a deviation. When investigation of the deviation reveals that a system is out of control, a thorough analysis should be performed and the system brought back into control. ~~Excursions out of temperature range defined by thermostability data or <659> should be addressed/corrected in order to prevent recurrence using a risk-based approach.~~	The proposed text seems to imply that "other" excursions—excursions within limits—may be repeated and do not need to be addressed. PDA suggests that USP revise the text to more generally recommend an approach in the QMS, consistent with the language in the other sections of this proposed chapter and <1079.2>.	