Mean Kinetic Temperature
Storage vs. Shipping and the Vagaries of Regulatory Requirements

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Monitoring production environments, storage facilities and distribution processes has become an important part of current good manufacturing practices (cGMP) within the biopharmaceutical industry. The FDA and other regulatory bodies have shown increased scrutiny in these areas and require accurate measurement and documentation.

As early as 1995, The United States Pharmacopeia (USP) recognized the need for drug storage standards and set out to identify compendial items for which storage and distribution were of special concern. They resolved to have proper storage and shipping instructions included with the compendial item so that the integrity of the product would be maintained until it was received by the patient.1

What resulted was the adoption of Mean Kinetic Temperature (MKT), a condensation of various proposals, discussions and decades of efforts, that calculates product degradation. In its simplest terms, MKT is a fixed temperature that simulates the effects of temperature variation over a period of time. It differs from other means such as a simple numerical average or arithmetic mean in that higher temperatures are given greater weight in computing the average. Disproportionate weighting of higher temperature in a temperature series, according to MKT, gives proper recognition to the accelerated rate of thermal degradation of products at higher temperatures. If a specific MKT is exceeded, a second calculation is used to determine the reduction in the product’s shelf life, and appropriate actions can then be taken. But MKT is much more than just a number. It is used to reference temperatures for stability studies, determine a product’s acceptable range of storage temperatures, and define “normal” storage conditions on the product label.

MKT: What it is, and What it is Not
Mean Kinetic Temperature is defined by the USP as “the 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. Thus, MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations. It is not a simple arithmetic mean. MKT is calculated from temperatures in a storage facility.”2

It’s not a perfect process by any means, and it is not without detractors, but it is the standard. The FDA states in its Code of Federal Regulations, Part 203 that manufacturers, authorized distributors of drugs and their representatives shall store and handle all drug samples under conditions that will maintain their stability, integrity, and effectiveness, and ensure that the drug samples are free of contamination, deterioration and adulteration.3 This is not possible without the application of MKT.

The European Union is more specific. Their Guidance on Good Distribution Practices states, “The quality system operated by distributors (wholesalers) of medicinal products should ensure that storage conditions are observed at all times, including during transportation. Products requiring controlled temperature storage should also be transported by appropriately specialized means.”4

Stability monitoring of medicinal products is an area also addressed by the International Conference on Harmonization (ICH) in their Technical Requirements for Registration of Pharmaceuticals for Human Use. Their final guidance, ICH Q1A (R2), Stability Testing of new Drug Substances and Products, issued in February 2003, has been widely adopted across Europe, Japan and the U.S. Section 2.1.6 reads in part, “A drug product should be evaluated under storage conditions that test their thermal stability. The storage conditions and lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use. Data from the accelerated storage conditions, and, if appropriate, the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as during shipping).”5

Health Canada’s Guidelines for Temperature Control of Drug Products during Storage and Transportation, Guide-0069, segregates Warehousing and Storage — “All drugs should be stored according to conditions described on the label” — and Product Transportation and Products in Transit — “the transport process and containers should prevent damage and maintain the integrity and quality of the drug products.”6

More Than One Way to Average
There are a number of interpretations of how MKT is achieved, including how many sample values are fed into the formula, whether the minimum and maximum samples are fed into the formula separately (as recommended by the FDA), whether the arithmetic mean is fed into the formula (as recommended by the USP and by the UK MHRA), as well as choices of the stability testing periods, frequencies and whether or not allowances are made for individual datum exceptions.

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No Panacea

USP General Chapter <1079> Good Storage and Shipping Practices recommends the use of MKT for establishing profiles of storage facilities. They do not, however, reference the use of MKT for determining the environmental effects (including light, humidity, oxygen and temperature) during distribution. The USP clearly states that determining the ability of pharmaceutical articles to maintain their Pharmacopeial requirements of identity, strength, quality, and purity through distribution may include, but is not limited to, the use of ICH stability studies, temperature cycling studies, stability shipping studies, ongoing regulatory stability commitment studies, market experience portfolios and product labeling commitments.7

Yet, there are a small number of manufacturers and shippers of temperature sensitive pharmaceuticals that rely solely on MKT calculations to justify their shipping methods and packaging requirements, thereby sending their products out in unqualified — and possibly inadequate — packaging, incapable of maintaining recommended storage requirements, and potentially putting their product at risk.

There are perceived loopholes in the Food Drug & Cosmetic Act, USP General Chapter <1079> and ICH guidelines, and vague and contradicting statements among the documents. Such ambiguities are subject to interpretation.

In what is commonly referred to as the “adulterated drug rule,” in The Food Drug & Cosmetic Act states, “A drug or device shall be deemed adulterated — if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”8 (The FDA defines and considers the holding of a drug as storage, distribution and transportation.)

While on the surface this seems to be a free pass to use MKT as the basis for making this determination, what is often overlooked is that the FDA cleverly relies on cGMP, as the basis for a drug meeting all the necessary requirements. But cGMP, as we know, is a forward-moving target.

The USP states in the current edition of General Chapter <1079> that determining the ability of a drug to maintain its original characteristics may be achieved by using ICH stability studies. And as we’ve seen, ICH QA1 (R2) confirms, “Data from the accelerated storage conditions, and, if appropriate, the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as during shipping).”5

However, ICH intermediate and accelerated stability studies call for six month storage at temperatures of 30º C and 40º C, respectively.5 They neither account for short-term temperature swings or spikes that often exceed these temperatures in the distribution environment, nor do they account for the cycling of temperatures that inevitably occur during transit.

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No “Get Out of Jail Free” Card

“Although MKT is a valuable tool, it cannot be used to replace the qualification of packaging materials and the validation of distribution processes. Companies must have an understanding of the hazards that exist in the transportation/shipping of pharmaceutical products,” said Mary Foster, Pharm.D., VP of Regulatory Compliance at Catalent Pharma Solutions, formerly Cardinal Health PTS. Dr. Foster is also the accountable committee member for the USP General Chapter <1079> revision committee. “We are recommending to the USP Expert Committee on Packaging and Storage, the final approving body, that they change the definition of MKT around when and how to use the calculation. That proposal is in the revision to Chapter 1079 now and is under the Committee’s review,” she remarked.

“It’s been my experience that companies don’t really understand MKT or they don’t apply it properly. It can give them a false sense of security because it was intended for long-term storage, not for shipping. It can’t tell you what happens to a product in distribution. And it’s difficult to stand in front of a regulator and say that MKT says our packaging is ‘good enough.’ How do you defend that?” Dr. Foster rhetorically asked.

She noted, “MKT’s simplified expressions of the overall effect during storage may miss temperatures in transport affecting the identity, strength, quality and purity, as well as safety and efficacy of the drug. Some products, like low therapeutic index drugs, become more potent as they degrade.”

Desmond Hunt, Ph.D., scientist in the Department of Standards Development at the USP, and scientific liaison to the Packaging and Storage and Parenteral Products – Industrial Expert Committee, agrees. “You can’t rely solely on the MKT of 12 months of storage data to tell you what’s happening to your product in an uncontrollable environment as varied as distribution,” he said.

cGMP

USP General Chapter <1079> is one of the leading documents referenced by the FDA and other regulatory bodies as the “go to” document for proper handling and distribution practices. But currently, it is under revision (as is Health Canada’s Guide 0069) and no one knows what the final decision of the Packaging and Storage Expert Committee will be when it comes to how and when to use MKT.

PDA Technical Report No. 39 Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature Sensitive Products through the Transportation Environment is another critical and often referenced document by regulators, including the FDA. In Section 4, “Product Stability Profile,” they make mention of the fact that transportation temperatures may differ from the conditions specified for long-term storage, and that the acceptable range is determined by performing product temperature excursion studies on a product-by-product basis. Only then do they advocate shipping “outside of respective label storage conditions,” for it provides the “stability data or the scientific / continued on page 30
technical justification to demonstrate that the product quality is not affected.” Technical Report No. 39 also makes special note that “It is not possible to control the temperature of product during the distribution process; therefore additional studies at anticipated extreme temperatures (e.g. elevated or freezing temperatures) should be performed. Long-term storage or label storage temperatures may be different from short-term shipping / distribution temperatures.”

This falls in line with the USP <1079> recommendation to perform cycling studies.

Of course, you can’t perform additional studies at anticipated extremes in temperature without knowing what those temperatures and durations are. The surest way to achieve that is by collecting environmental data from the distribution environment. It also provides documentation that the shipper has an understanding and control of the distribution process and can monitor the process for system changes that may affect the quality of the product.

With international regulatory agencies trending toward label storage conditions as the basis for accepting product shipments and requiring documentation to prove it, it appears that the use of MKT will return to where it was originally intended: for compounding drug products and determining long-term storage conditions — unless the USP has other ideas.

References

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