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REGULATORY SCIENCES

AAPS ELEARNING

Advanced Computer Modeling Seen as Way to Dissect Drugs' Complex Effects

PHARMACEUTICAL STABILITY:

Doing the Right Thing versus Doing Things the Right Way

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The Regulatory Sciences section submitted this article.

Standards and approaches to stability testing in a global setting

Stability is a critical quality attribute of all pharmaceutical products, and stability testing is a crucial aspect of the drug development process, with stability data as the foundation of the chemistry, manufacturing, and controls (CMC) part of any marketing application. Without an expiry profile that is suitable for the intended distribution, a drug product will go nowhere regardless of how stellar its other attributes are.

The stability studies of drug development encompass several factors that affect the expiration dating of drug products. These include chemical and physical stability during the preclinical formulation stages, recommended storage conditions, process development, packaging development, and postmarketing life cycle. Ultimately, sponsors rely on their stability data to gain regulatory approval for expiry dating for their marketed pharmaceutical products.

Many guidelines have been promulgated by regulatory authorities on the subject of stability; however, the topic is hardly static, since issues are continually raised and practices challenged. Regulatory thinking also changes.

For example, the Food and Drug Administration (FDA) withdrew its stability guidance in 2006 because some of the principles were inconsistent with the agency's 21st century initiatives. More recently, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) withdrew its Q1F guideline on storage requirements for Zone III and IV. As a consequence, the regulators of several countries and regions have now revised their own stability testing guidelines.

These changes lead sponsors to search for the right choice of stability storage conditions for global submissions. Although various regulatory agencies have derived their stability testing requirements from parent ICH guidelines, they may differ in some parameters of stability testing requests[1] (i.e., stress testing, selection of batches, container closure systems, specifications, storage conditions, testing frequency, stability commitment, evaluation, statements, and labeling). Furthermore, the minimum time period to be covered by data at the time of marketing application submission can differ and remains a cause for much debate.

CONTROLLING STABILITY

Although the regulations do not provide widespread requirements for running distribution stability studies for shipment of pharmaceutical products per se, regulatory agencies expect the manufacturer to understand its product's stability profile thoroughly and to maintain vigilance while the product is in distribution. Regardless of the recommended time period to be covered by data at the time of filing, a sponsor can still fail to meet the most stringent global regulatory reviews. Before a sponsor decides how much data it requires, when, and for where, it is vital that it understands the nature of its product.

THE UNITED STATES, EUROPE, AND ICH

In 1998, FDA defined stability as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality, and purity throughout the retest or expiration dating periods.[2] As noted, FDA withdrew this guidance and adopted ICH Q1A(R2) to supercede it.[3]

Notwithstanding these changes in guidance, physical, chemical, and microbiological data are still generated as a function of time and storage conditions (e.g., temperature and relative humidity). Stability testing requirements are now more globally harmonized, but parameters—such as stress testing, container closure systems, testing frequency and evaluation—can differ, affecting labeling. Furthermore, variance still exists regionally, most notably

Table 1: Selection of Batches and Storage Conditions

Parameters	ICH/FDA/European Medicines Agency (EMA) [CPMP/ICH/2736/99-ICH Q1A (R2)]	EMA (CPMP/QWP/122/02 Rev.1)
Selection of batches	Drug product: Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified.	Option a: Drug product: For conventional dosage form and when drug substances are known to be stable, stability data on at least two pilot scale batches are acceptable. Option b: Drug product: For critical dosage forms or when drug substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be of at least pilot scale; the third may be smaller.
Storage conditions	Drug product: The long-term storage conditions should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life.	Drug product: The long-term storage conditions should cover a minimum of 6 or 12 months duration for option a or b, respectively, at the time of submission.

in the selection of batches and minimum time period covered by the data required at the time of filing (see Table 1).

Formal stability testing using different temperatures and humidities provides evidence that the quality of a drug product under the influence of various environmental factors might change with time.[2] Although storage conditions are relatively constant, the distribution and in-use environments can vary greatly, especially when a drug product is shipped between various climatic zones. Seasonal changes, mode of transportation, the number of distribution stops along the way as well as repackaging are variables that need to be be taken into consideration when developing a study protocol to generate sufficient and appropriate data.

To pass regulatory scrutiny, it is generally advisable to include a minimum of 12 months of long-term supporting stability data with 6 months accelerated. Examples where exceptions might occur are for Europe (see Table 1) and might also include special circumstances (e.g., a drug product being developed for an unmet need).

From a regulator's point of view, sufficient data depends upon the nature of the drug product and various stability study strategies and intentions, the temperature conditions employed, the analytical methods in play, and how data analysis is handled. For example, a product that is devoid of out-of-specification results is likely to require less ancillary data to satisfy a health authority than a product that exhibits concerning trends.

NON-ICH COUNTRY REQUIREMENTS

In regards to global stability, the United States is only one market (albeit a major market) of the pharmaceuticals-consuming world. When determining conditions for stability testing, real-world conditions should be considered, keeping in mind that not all countries follow U.S. patient dispensing practices. These include what happens after a unit of packaged drug product is opened and stored in less-than-optimal conditions.

Optimal conditions in the distribution chain may not exist at all in countries of climatic Zones III and IV. For example,

India has microclimates ranging from alpine tundra and glaciers in the north to desert in the west to the tropical regions of the southwest[4] (also discussed at the AAPS-sponsored conference *Pharmaceutical Stability Testing to Support Global Markets,* cosponsored by CHPA, EAS, GphA, and PhRMA, September 10–12, 2007, Bethesda, Md.). Unequivocally, this is not unlike the United States. Packaging systems and stability testing should take all climatic variations into consideration.

The ICH guidelines cover the stability requirements of the ICH region (United States, European Union, Japan, and observers). However, 80 percent of the world's population lives in nonparticipating countries. The World Health Organization (WHO) *Guideline on Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical products No 953 2009 Annex 2*[5] is recognized by these countries' regulatory authorities.

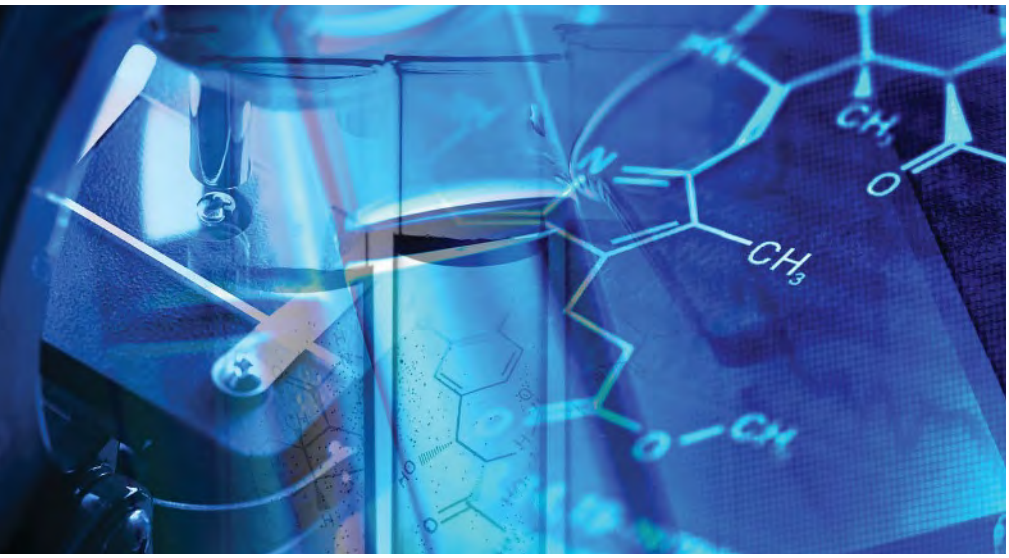
Many of these markets have issued their own guidelines, and the WHO documents reflect those conditions by footnoting with reference to regional harmonization groups—such as Association of Southeast Asian Nations, ICH, and Global Cooperation Group—and official communications from national medicines regional authorities. Implementing country-specific stability requirements can potentially become a liability, since stability studies may have been established to meet the original requirements only to have new rules established without a transparent promulgation process.

SUPPLY CHAIN REALITY

The time a product spends in transit and/or in storage at third-party warehouses, including excursions during transit, are the situations that are outside the normal purview of stability testing. One can start with the ICH guidance, for which there are several models for predicting shelf life after a temperature excursion. Conversely, finding the trigger for what constitutes an excursion can vary from one location to another, as different regions require the use of different models and methods for prediction.

Drug products requiring controlled-temperature storage conditions must be distributed in a manner that ensures that the product quality will not be adversely affected. For example, in ICH Q1A (R2), "Stability Testing of New Drug Substances and Products,"[2, 3] it is stated that data from accelerated stability studies can be used to evaluate the effect of short-term excursions that may occur during the shipping of drug products. With the exception of short transit times within the same climatic zone, it is virtually impossible to validate a shipping method against all environmental scenarios.

The nature of excursions for which the potential temperature is outside of the



labeled storage conditions also needs to be well thought out, and the effect can be evaluated in terms of the stability analysis for that drug. As noted, in the United States, Europe, and Japan, the stability program approach is typically designed on the basis of the information provided by the development and routine ICH Q1A stability provisions.[3] However, four-fifths of the world's population lives in markets outside of ICH, where the global supply chains and distribution environments are highly variable. As such, a stability program should be established that reflects these variables to facilitate a true stability profile for each product.

Inherently, stability protocols for distribution could be developed by considering the product characteristics and representative environmental conditions, anticipating environmental extremes by foreseeing stressful environmental conditions, and demonstrating higher and/or lower temperature excursion than what is expected to occur during the product's supply chain life cycle. Such a stability approach will increase the chance of success for marketing approval, perhaps even allowing less restricted labeling.

These combined data should produce the information necessary to develop product-specific shipping criteria. In turn, these criteria could be used to design a shipping document (i.e., control strategy document) that confirms the product's robustness through distribution and in-use. The data also functions to validate and specify the acceptable transit time limits and temperature ranges and provides controls for distributing a product both domestically and globally.

As discussed briefly above, the exact number of short-term temperature and thermal cycling excursion studies required depends upon anticipating the extreme temperature (e.g., distribution warehouse or regional climate) and the expected in-use conditions (e.g., repackaging, patient pill box, etc.). Formal stability studies can then be designed on the basis of storage classifications per *United States Pharmacopeia* recommendations: controlled room temperature, cool, refrigerated, and frozen.

These are also well documented and accepted in ICH Q1D, "Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products."[6] Upon the completion of such studies, samples could then be subject to long-term stability testing regional conditions to verify that the exposed product meets shelf-life requirements.

IN-USE AND ADMINISTRATION ROUTE

Before laying out a stability approach, it is vital to understand the nature of the dosage form and delivery system requirements (the route of administration and delivery system). Even if there is a diversity of testing in place, these choices have a significant impact on the stability data, which can still fail to meet the most stringent regulatory reviews.

Regarding in-use, many physicians may prescribe a stronger dose, instructing the patient to split the tablets, for example, thus saving on prescription costs. What is the effect on assay with a split tablet over time?

Moreover, distributors repackaging oral solids from a larger bottle to smaller containers or even blister packs may not provide the same shelf life as determined by products that were tested in-house in the approved container closure system. If results from routine studies indicate that the product stability profile is very stable, then one may decide that distribution studies are not warranted.

From a regulator's point of view, all dosage forms are evaluated for appearance, assay, and degradation products. Additional tests are needed for specific dosage forms. For example, proof of sterility is required for parenteral products but not for oral dosages.

Studies of drug products for injection (i.e., parenterals) include monitoring for clarity, color, reconstitution time, and residual moisture content. The stability of parenterals must also be evaluated after reconstitution or dilution in larger volume parenteral solutions, according to the label instructions.

Studies for drug injectable suspension also include particle size distribution and redispersibility properties. The studies for drug injectable emulsion products also include phase separation, viscosity, mean size, and distribution.

Small volume parenterals are a wide range of injection products (e.g., drugs for injection, drugs for injectable suspension, and drugs for injectable emulsion). Large volume parenterals (LVPs) studies ensure that absorption and adsorption during dwell time do not occur.

Some LVPs are designed for multiple use. These products are evaluated for stability and preservative efficacy after opening with part of the content removed. In-use studies can typically last from several days to more than a few weeks.

The functionality and integrity of parenterals in prefilled syringe delivery systems

needs to be evaluated throughout the expiration dating period with regard to factors, such as the applied extrusion force, syringeability, pressure rating, and leakage. Continued assurance of sterility for any parenteral product is by a variety of means, including evaluation of the container and closure integrity.

The evaluation of inhalation powders and liquids[7] in contrast include aerodynamic particle size distribution of the emitted dose, microscopic evaluation, compatibility of the container/close system or delivery device, microbial limits, moisture content, foreign particulates, content uniformity of the emitted dose, and number of doses per device that meets content uniformity of the emitted dose. The unique characteristics of metered-dose and dry-powder inhalers can affect the product's efficacy as well as the product's ability to deliver reproducible doses. These factors must be considered during development with respect to formulation, stability, manufacturing, container and closure system, and quality control.

Stability data for products supplied in closed-end tubes (e.g., creams or ointments) should support the maximum anticipated use period after the tube seal is punctured, allowing product contact with the cap. Evaluation of ophthalmic or optic products (e.g., creams, ointments, solutions, and suspensions) includes sterility, particulate matter, and extractables. Evaluation of nonmetered topical aerosols includes appearance, assay, degradation products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, preservative efficacy, spray pattern, water content and particle size distribution (for suspensions).

THE TAKEAWAY

The complexity of the distribution chain requires an understanding of the interdependency between related processes and product characteristics, in addition to the ever changing regulatory climate in the destination markets. The pharmaceutical industry and regulatory agencies recognize that drug products may be subjected to excursions during the distribution and in-use period.

As some companies are turning to contract manufacturing organizations for their analytical testing, managing development of a project now also imposes organizational as well as technical challenges. Pharmaceutical products should be distributed in a manner that ensures products will not be adversely affected by environmental conditions on the basis of product stability, product history, packaging information, and the transport system used.

Stability is an integral component of a regulatory program, and a comprehensive testing regimen includes a global approach and a broad scope of analytical evaluation. Company personnel (e.g., stability experts and supply chain personnel) must share information. The importance of assuring the physical and chemical properties early and throughout development and commercialization is key to effectively managing resources and costs. The inclusion of a well-designed stability program in the development pathway can help alleviate time consuming regulatory pitfalls and facilitate a cost-effective process.

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DISCUSSION POINT

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My company plans to file a marketing application globally for a new product for which study conditions and the amount of stability data available at the time of filing may be an issue. How much data do we need to satisfy health authorities' expectations, when does it need to be available, and are there opportunities to update the applications during the review?

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