DPT Thought Leadership
Issue 15

PUTTING STABILITY UNDER A MICROSCOPE — 6 KEY COMPONENTS

INTRODUCTION

Stability plays a significant role in the life of a drug product. A drug must remain potent and safe long after it leaves a manufacturing facility. According to the ICH Q1A guideline, "the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions."

In short, stability testing exists for two reasons – to establish and/or extend the shelf life of a drug product and to provide information about the impact that packaging has on a drug product. This paper defines stability testing, discusses the recent increase in oversight by regulators, and establishes the six key components that reflect best practices of a robust stability testing program.

Stability testing takes place at various stages of drug development, each with a unique purpose:

- **Development – supports formulation development, safety and efficacy claims of investigational new drugs**
- **Registration – ascertains quality and shelf-life of drug product in intended packaging configuration**
- **Post approval – ensures quality of production and supports site or other changes to product**

There are three levels of testing: forced, accelerated, and real-time stability.

In forced-stability testing, the compound is exposed to a harsh environment, such as high temperature or humidity. This temperature often verges on the melting temperature of the active pharmaceutical ingredient (API). Forced-stability can also include testing under intense light. The results can be used to make predictions about reaction kinetics.

Accelerated-stability testing is less harsh. It can include temperatures up to 50°C, to predict what might happen to a drug at room temperature over an extended period of time.

Real-time stability testing requires storing the drug at room temperature, under natural light and expected levels of humidity in the areas where the drug will be sold. These tests often run for years. In addition, real-time testing must include potentially damaging scenarios.

Problems with stability can be rooted in temperature, humidity, photosensitivity, shaking, chemical interactions

and irradiation. Additionally, stability tests must be conducted on the API, other formulation components (excipients and intermediates), and interactions with packaging. The extended timelines and multitude of factors to test make it a complex undertaking, one that can serve as a mystery to many companies.

THE FDA CARES ABOUT STABILITY – SHOULD YOU?

Though previously overshadowed by more visible parts of drug development, the FDA his increased its oversight on stability testing, issuing updated guidance for drug applicants. They recently stated generic drug makers filing an ANDA as well as drug master files should give six months of data for stability testing, including both long term and accelerated conditions. This move to six full months of stability data doubles the prior requirement.

Evidence of increased regulatory oversight is found in the number of observations and warning letters citing stability testing. A March 2013 survey found a threefold increase in warning letter observations for stability testing from 2011 to 2012. In some warning letters, stability testing was unable to determine the expiration date for drug products. Other warning letters noted the company had no stability testing – period.

It is clear the environment surrounding stability testing has changed. Prior test methods are no longer sufficient to assess essential stability features of drugs or to determine the right storage conditions and date of expiration. Properly conducting these tests requires a range of technologies and applications. Following legacy testing processes and complying with previous guidance is no longer an option. The cost of failing to embrace the new guidance will be unwanted delays and higher costs to your drug development program.

Let's dive in to the six key components that make up a robust stability testing program:

#1: ACTIVE SUBSTANCE TESTING

In the development stage, stability testing is conducted on various elements of a formulation, including the API, excipients, and intermediates. Compounds are often removed from formulation at this stage because they are too unstable to be commercially viable. Detailed understanding of formulation ingredient stability is an integral piece of a systematic approach to stability evaluation.

One way to reduce stability risk in development is to select APIs and excipients listed in the USP-NF pharmacopoeia monograph, a listing of ingredient details that have been previously tested and whose interactions are well known and understood.

Selecting known substances reduces the amount of stability testing necessary at this stage. For APIs described in an official pharmacopoeia monograph, a manufacturer simply needs to:

- **Confirm the active substance complies with the pharmacopoeia monograph immediately prior to the manufacture of the pharmaceutical product, or**
- **Demonstrate the active substance is from a named source of supply**

For APIs not described in an official pharmacopoeia monograph, more complex stability studies are required that examine physical, chemical, biological and microbiological attributes.

#2: STORAGE CONDITIONS

Stability testing is conducted separately on both drug substances and drug products. For the general case, ICH Q1A states " … a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use."

The parameters for each storage condition are identical with respect to temperature, humidity, and time in storage. Additional guidance is provided for drug substances intended for storage in a refrigerator or freezer and for

drug product packaged in impermeable or semi-permeable containers.

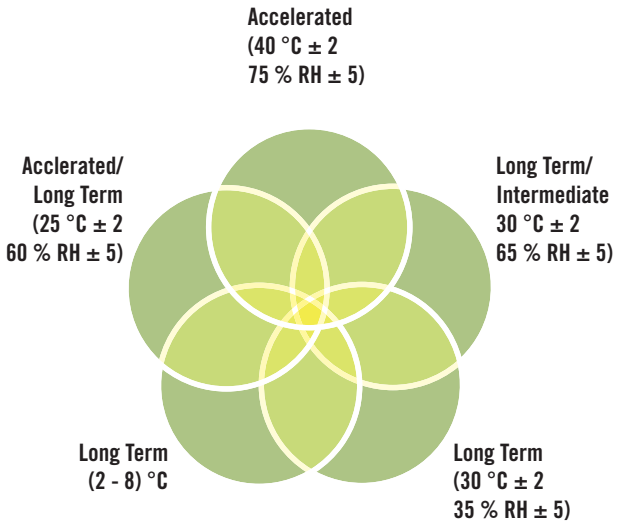
The three types of storage conditions are:

- **Long term**
- **Intermediate**
- **Accelerated**

The long term storage condition should, at a minimum, cover at least 12 months and three or more primary batches at the time of submission. Testing of the long term condition should continue for a period of time sufficient to cover the proposed re-test period.

The accelerated storage condition simulates long term stability in a compressed timeframe and is used as an indicator of expected future stability prior to submission. The long term storage condition results post-submission are used to verify whether the accelerated storage condition test was an accurate proxy for the actual long term storage condition.

Below is an illustration of the various storage condition parameters used in stability testing, including refrigerated products:



The intermediate storage condition is not always required and is a function of the environmental parameters used for the long term storage condition. Use of the 30°C parameters for long term storage alleviates the need for testing of the intermediate storage condition. Likewise, if the 25°C parameter is used for the long term storage, intermediate storage condition testing is only required if "significant changes" occur at any time during 6 months of testing the accelerated storage condition. Essentially the intermediate storage condition serves as a backstop if the lower temperature long term storage parameter is used AND if changes are detected during the six months of accelerated storage condition testing.

Additional guidance is found in ICH Q1A for drug substances intended for storage in a refrigerator or freezer and for drug product packaged in impermeable or semi-permeable containers.

#3: FREQUENCY OF TESTING

The frequency of testing varies with storage condition and is used to establish the stability profile of the drug product. ICH Q1A gives the following frequency guidance for products with a proposed shelf life of at least 12 months:

Long term storage condition

- **Year 1 – every 3 months**
- **Year 2 – every 6 months**
- **Year 3+ – annually through proposed shelf life**

Accelerated storage condition

- **Minimum three time points, including the initial and final time points (e.g., 0, 3, and 6 months)**
- **6 month study is recommended**

When a reasonable expectation exists that results from accelerated testing are likely to approach "significant change" criteria, testing frequency should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

Intermediate storage condition

When testing is required as a result of "significant change" at the accelerated storage condition:

- **Minimum four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months)**
- **12 month study is recommended**

#4: IN-USE STABILITY TESTING

The purpose of in-use stability testing is to establish the period of time during which a multi-dose product can be used while retaining acceptable quality once the container is opened and the first dose is removed. According to ICH Q1A, information from in-use testing provides information for labeling on the preparation, storage condition, and in-use period of the product.

Testing should include:

- **2 or more batches**
- **Pilot scale or greater production**
- **1 or more batches tested near end of shelf life**

If full shelf life test results are not available prior to submission, one batch should undergo in-use testing at the final point of the submitted formal stability studies.

#5: VARIATION TESTING

Because stability testing exists for two reasons – to establish and/or extend the shelf life of a drug product and to provide information about the impact that packaging has on a drug product – testing does not stop.

Thus far, stability requirements have focused on milestones along the journey to drug product approval including, new product registration, process validation, and annual commitment batches.

Once a drug product has been registered, additional stability studies are required whenever major variations are made. Examples of this include:

- **Formulation change**
- **Raw material manufacturer change**
- **Primary packaging material manufacturer change**
- **Reprocessing batch**
- **Batch size change**
- **Manufacturing process change**
- **Machine change**
- **Site transfer**

#6: ONGOING STUDIES

As seen above in the Variation Testing section, stability testing does not cease after a product gets to market. An ongoing stability program monitors and determines that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label.

A robust ongoing stability program should be detailed in a written protocol with results presented in a formal report. At a minimum, the program should include the following parameters:

- **Number of batches and batch sizes, if applicable**
- **Relevant physical, chemical, microbiological and biological test methods**
- **Acceptance criteria**
- **Reference to test methods**
- **Description of the container closure system(s)**
- **Testing frequency**
- **Describe conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labeling, should be used)**
- **Other applicable parameters specific to the API**

Ongoing studies can support shelf life extension by documenting stability data (for the proposed interval) for three batches that meet all following criteria:

- **Same product/potency**
- **Same manufacturing process**
- **Same primary packaging material**
- **Same formulation**
- **No significant change in the manufacturing procedure**

Shelf life may be extended as long term data becomes available to justify the extension.

CONCLUSION

As detailed above, stability testing is a multi-faceted, complex endeavor. Even more alarming is the increased oversight by regulatory agencies in the last two years. The combination of these two facts poses a real threat to pharmaceutical companies that do not devote the necessary attention and discipline to this aspect of their efforts.

As with other areas of drug development, the old saying "pay now, or pay later" holds true. Taking shortcuts with stability testing is not an option. Any perceived savings of time and money in the near term will be lost as the cost of a regulatory inquiry or warning halts your project.

When it comes to developing and manufacturing semi-solid & liquids as well as complex solid dosage forms, no challenge is too difficult; no solution is too elusive. DPT Labs offers expertise that simplifies the complexities of stability testing.

To discuss your stability testing needs and how DPT Labs can help, contact us at http://www.dptlbs.com/contact-us or call 1.866.CALL.DPT.

ABOUT DPT LABORATORIES:

DPT is a contract development and manufacturing organization (CDMO) helping pharmaceutical companies achieve clinical and commercial success. Through our specialized Centers of Excellence, we're tenacious about discovering solutions. We ask the right questions and thoroughly investigate your options. Our experts give you the answers you need from development through commercialization. We bring vast experience in resolving development and manufacturing challenges in sterile and non-sterile semi-solids & liquids. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

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