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STABILITY TESTING AS A QUALITY CONTROL MEASURE:

Optimizing the Process throughout the Product Life Cycle

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Yunhai Xiao, M.S.
Director, Analytical Services

Guoqiang Dong, Ph.D.
Executive Director, Analytical Services of CMC

Kang Wang, Ph.D.
VP, Analytical Services

Dongmei Wang, Ph.D.
Executive Vice President, Global CMC Services

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Stability testing is, in essence, a quality control process and is therefore a vital component of every phase of clinical development for both large and small molecules – from early phase through to and including post approval. It should be treated as an ongoing program rather than as a periodic exercise.

Assessing a drug product's stability is a complex and lengthy process with objectives and methodologies varying by the development phase. A poorly designed stability study can cause delays that extend to years, create budget overruns in the tens of millions of dollars, and even result in product failure. Thus, stability testing requires scientific expertise and very specialized experience in order to minimize development costs and avoid severe consequences.

STABILITY TESTING IS AN ALMOST CONTINUOUS PROCESS *THROUGHOUT A PRODUCT'S LIFE CYCLE.*

The following paper serves as an introduction to the purpose, scope, and type of stability testing required at each phase of product development. With this understanding, sponsors can aim to optimize the process and ensure that the right data are gathered at the right time.

The Multi-Purpose Stability Program

According to the International Con on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 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."

Stability tests, which are performed in specialized labs, are undertaken to:

- Identify and understand the conditions that cause product degradation
- Ensure that a product remains stable through the course of a clinical trial
- Recommend storage conditions and packaging solutions
- Determine labeling instructions concerning storage
- Predict and establish a product's shelf life for commercialization
- Demonstrate to regulators that the manufacturer's quality systems are, in fact, working

Thus, the results of stability studies directly influence formulation, manufacturing, and storage decisions and support the goal of ensuring that quality, efficacy, and safety are built into the drug product.

A Slow and Painstaking Process

Stability testing follows a complex set of procedures that involve considerable time, scientific expertise, and cost. Assessments take months and years to complete, even when the plan is expertly streamlined, and some tests are performed in parallel. The US Food & Drug Administration (FDA) requires twelve months of stability data as part of the new drug marketing approval package, and commitments of two to three years of shelf life stability.

Data accumulate over the life of the product and necessitate extensive statistical analysis. While the process moves towards greater accuracy and precision as the product continues through development, there can be setbacks that make it a non-linear proceeding. For instance, a stability issue may be discovered many months down the road, requiring that the product be reformulated, and that testing is repeated again. So, the process can be iterative, as shown in Figure 1.

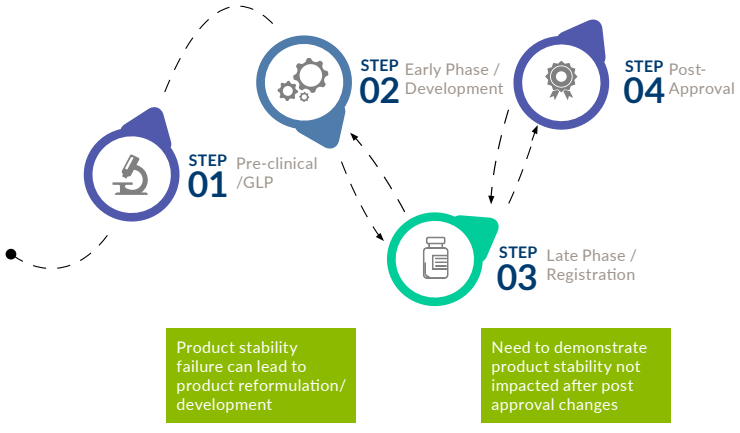

Figure 1, Iterative Process of Stability

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Testing Across the Life Cycle

Stability testing is an almost continuous process throughout a compound's life cycle. However, the testing requirements change as the product progresses through development and into the marketplace in the following ways:

- The product specification limits change from reporting open-ended results to needing to fall within specific limits that tighten as more data are available. Increasing robustness and precision are required each succeeding phase.
- The level of validation required for the method increases with each phase.
- The need for scalability increases with each phase.

Table 1 illustrates the type of stability required at each phase of development.

CONTINUITY IN A LAB PARTNER ACROSS THE DEVELOPMENT TIMELINE ALLOWS KNOWLEDGE TO ACCUMULATE WITHOUT INTERRUPTION

Product Development Cycle			
Pre-Clinical/GLP	**Early phase/development**	**Late phase/registration**	**Post approval**
Stress study to understand the compound and degradation pathway Drug substance stability, dosing formulation stability to support GLP dosing study Usually short period of weeks Include key quality tests for the specific dosage form Method development is targeted to the purpose of the test, method validation is minimal as method will most likely change in later phase. Usually open specification "report results"	Support formulation development, Use stress condition for lead formulation selection Support early-phase clinical trial, time enough to cover clinical studies Continue to understand product formulation, API excipient reaction, optimize formulation, manufacturing process, container closure, package configuration Accelerated and long-term storage conditions to estimate shelf-life Demonstrate special stability for clinical trail - In-use study to mimic clinical use of the product Freeze-thaw study to demonstrate product freeze-thaw storage effect on product quality Shipping study - evaluate potential product quality change during shipping Photo stability - evaluate product stability when exposed to light Developing stability indicating method to monitor the quality attributes of the API/ product over time. Set initial specification, continue to tighten the specification when there is more knowledge about the product	Formal stability study for product with final routine of synthesis of API, product formulation, manufacturing process, packaging Accelerated and long-term storage conditions following ICH Q1A guidelines Full validation of stability indication methods, including intermediate precision, robustness, and other studies Resolving upcoming issue during validation such as unknown impurity identification, leachable study All final specifications are justified with supporting data	Continue to demonstrate product qualify, support manufacturing site or other changes to products Need to go through similar stability as in registration phase for any change Need to meet any new requirements from regulatory for product safety

Table 1: Stability Tests across the Product Life Cycle

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Devising a Study Protocol

Study optimization begins with thoughtful development of the protocol so that the necessary insights are gained at the right time. Well-designed studies inform the next phase of development and the next set of required tests.

At a high level, the tests are designed to measure critical quality attributes, and the factors that must be considered in developing a stability protocol such as:

- The dosage form (liquid, injectable, solid, semi-solid, etc.)
- Batch selection
- Packaging options, use of a desiccant (if so, what kind and size)
- Storage conditions, including temperature, humidity, physical orientation and the various (usually multiple conditions are tested simultaneously)
- Testing intervals (when to pull the sample from the stabiity chamber for testing)
- Stability specifications (pass/fail acceptance criteria)

Although the study protocol is unique to each compound, experienced laboratories have a base of knowledge upon which to build as they make the study design decisions for any individual product. This, of course, eliminates much trial and error and speeds the entire process.

Early Phase Testing: Preliminary Data

In early phase research, only limited testing is necessary, as the object is merely to get a first impression of the degradation pathway and the formulation's stability. Primarily, the results will reveal whether the formulation is sufficiently stable for early-phase clinical research or if it needs to be changed. It is nonetheless important to use these early studies to identify as many issues as possible before resources are invested in a direction that later proves to be unworkable. So, while only limited testing is necessary, the protocol for that testing must be done right.

The immediate goal is to ensure that the product will last for the duration of the trial and to establish when the product will need to be retested. The testing will need to cover all of the critical quality attributes and storage conditions. However, the container and packaging options need not be studied this early. This may require only 3 to 12 months of stability data, depending on the length of the early-phase trial. If the results show that the product is not sufficiently stable, it must be reformulated and the whole process restarted.

At this point, every batch of the compound is tested for stability, and the data compiled, to gradually add to a base of knowledge that can be used later in proposing an expiry period.

Early-Mid Phase Testing: Continued Refinements

As the product progresses along the development pathway, more tests are added, and greater precision is sought. The focus at this point should be to acquire a deep understanding of the product's stability and to support scalability through greater manufacturing capacity. Multiple formulations and product strengths may be evaluated based on the information gained during earlier phase studies to further refine the formulation. This could require 12-24 months of stability data.

Case Study: Stability Studies as a Quality Control Process

During the course of a stability study on an oral solution drug,analysts observed that an unknown impurity increased rapidly. The impuritylevel climbed over 0.5 percent, causing a great concern for the sponsor, as it was preparing for an ANDA submission.

Frontage quickly modified the HPLC analytical procedure used during the stability study for LC/MS/MS analysis. Frontage scientists were able to successfully isolate the unknown impurity,propose its structure based on the LC/MS/MS data, and confirm its final structure with NMR (C13 and H1) studies.

Through a stress study, they discovered that light and oxidation were the major degradation pathways to the impurity. Based on this, they recommended a modification to the product packaging.

As the isolated impurity possessed a strong UV chromophore, RRF was determined. Following RRF correction, the actual impurity level was only around 0.1 percent, an acceptable level. The sponsor subsequently submitted the stability data to the FDA as part of the ANDA, and the agency raised no questions regarding the unknown impurity.

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Late-Phase Testing: Preparing for Registration

By Phase III, a large body of stability data should be accumulating, but more is required to:

- Confirm that the established stability is not affected by the commercial manufacturing facility, equipment, and materials
- Select the packaging components—the container, the container closure, and outer packaging (photo-sensitivity testing is required at this stage)
- Finalize a shelf-life recommendation
- Support an application for marketing approval

Regulators aim to ensure that products will meet the shelf-life expectations and that the product's effectiveness will not be compromised over its expected life. The FDA requires that the registration batch be tested and that a minimum of twelve months of data be submitted to support shelf life and storage claims. And, for certain dosage forms, such as semi-solids, suspensions and solutions, the FDA also requires data on leachable and extractable studies on the packaging materials in contact with the products.

Post-Approval Testing: An Ongoing Quality Check

Once a product is marketed, stability testing continues as a means of monitoring product quality and to ensure that the assumptions made in the clinical trial process stand the test of time. Any post-approval changes in the manufacturing process must be shown to not affect stability. Regulators require that a certain representative sample of production batches be tested on an ongoing basis.

Capabilities of a Lab Partner

Because a stability program grows more robust with time as more and more data are collected, it behooves sponsors to retain the same lab partner across the development timeline and into commercialization. Such continuity ensures that the body of knowledge that has been building about the product accumulates without interruption and is put to best advantage at each stage along the way. Qualified labs will be those that:

- Comply with Good Manufacturing Process (GMP) guidelines established by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for human Use (ICH) and regulatory bodies
- Are equipped with the latest instrumentation for a full range of testing, including API/Product release, stability, and dissolution tests
- Have demonstrated experience in testing multiple dosage forms
- Demonstrate a long history of business stability and a track record of success
- The ability to reformulate a compound

Conclusion

Stability testing is a lengthy and complex process that requires considerable expertise to avoid costly complications and setbacks. By approaching stability testing as an ongoing part of the quality control process that is best performed by the same lab partner throughout the product life cycle, sponsors stand to streamline the process and take advantage of the rich data accumulated.

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