Stability Program Design and Management

Due to the length of time required to conduct stability studies and obtain requisite data, stability program management requires diligent integrated planning and oversight. We are well versed in the regulatory requirements and statistical processes required to support commercially viable product expiry periods. This includes the ability to design stability studies, analyze results, and compile and effectively present the data.

Points to consider when using a contract stability lab

How many times have you read a stability article and all it provided was the information specified in the ICH guideline? It's enough to make you pull your hair out before you have turned the first page.

We focus on the start-up and set-up of a stability program when it must be outsourced to a third-party laboratory.

We review stability programs from the standpoint of effective program management.

- Initial communications with your contract stability organization
- The transfer of your methods
- Required product knowledge and program management
- Data presentation for important decision making on label claims

How to Optimize Your Stability Program At Each Phase Of Drug Development?

- Stability is a full-time job.
- Stability-indicating methods are developed early.
- Make API substance stability part of molecular characterization.
- Stability work is continued through all phases of development.

COMMUNICATIONS — THE FIRST STEP

Some specific items for discussion:

At each phase of development (preclinical, early/mid-clinical, and late clinical) are elements that can increase the probability of obtaining useful data to make critical decisions and gain FDA approval.

Preclinical Development: Make Stability Part of a Go/No Go Development Decision

The purpose of this phase is to understand and characterize your drug substance by conducting appropriate testing for identity, strength, purity, and stability. Stability is key before you even get into the clinic. The only reasons for a chemistry, manufacturing, and controls (CMC)-based clinical hold at investigational new drug (IND) Phase 1 are a safety concern or insufficient information to assess safety.

The way to mitigate stability as a safety concern is to:

- Have plenty of technical data.
- Perform short-term, real-temperature, and accelerated stability of the active pharmaceutical ingredient (API)/drug substance (DS) and experimental drug product (DP), if available.
- Assess the stability of the test article and test article in a carrier during pivotal preclinical trials, as required by the regulations.

Properly structuring your stability program at this stage allows for a detailed understanding of the profile and characteristics of the drug substance. It is on this foundation that subsequent stability testing will be built for eventual product approval.

Early to Mid-Clinical Development: "Do Your Homework" — Acquire Deep Stability Knowledge

The FDA notes "it is helpful if the stability protocol is submitted in an information amendment before or during Phase 3 studies and is discussed at the end-of-Phase-2 meeting."

At this stage, the stability program should be in full swing. To best position yourself for successful late-phase clinical development, it is important to:

- know degradation pathways, kinetics, and products of API/DS and DP to optimize stability-indicating methods for DS and DP and get them ready to validate or re-validate
- show stability of materials used in clinical trials
- develop primary and working reference materials
- fully characterize any degradants seen in real-time/temperature studies and primary accelerated studies (any studies used to establish/justify expiration date/shelf life)
- evaluate container/closure systems
- develop stability specifications and finalize them before the manufacture of Phase 3 material.

Late Clinical Development: Phase 3 — Full GMP Compliance

During this phase, not only is stability performed on the API/DS, drug product intermediate (DPI) (as applicable), and DP, but also stability of diluents, reconstituted drug product, and drug product in multi-use containers (e.g., vials) must also be performed.

Work performed at this stage enhances the chances of getting an approval letter (rather than a "complete response" letter). Phase 3 requires GMP-compliant protocols, validated methods, change control, and well-documented investigations of all deviations, discrepancies, and out-of-specifications (OOSs).

There is a high risk of failure at this stage. The company's commitment to quality will be evaluated here, specifically, in what you do when things go wrong (i.e., how effective you are at documenting and handling such events). Ensure success by having robust OOS, investigation, corrective and preventive actions (CAPAs), and deviation systems, and rigorous training on their execution. To this end, stability reports should include:

- general information
- summary information
- specifications and test methodology
- study design and conditions
- data and data analysis
- degradation product information
- conclusions

It is also important to include references to any deviations and/or OOS documentation. Reports should be clear and concise; include the rationale for the design, statistical handling of data, and specific conclusions to help inspectors or auditors understand the connectivity of the data to the overall development of the drug. Do your due diligence instead of waiting for the FDA to do it. Find out where the gaps are, acknowledge those gaps, and put a plan in place to mitigate them.

This also is the time to prepare for an FDA inspection of your stability program. The easier you make it for an inspector to follow your drug development road map and the better you explain how stability data supports decisions made, the less likely you will have something appear in any 483s.