



Outsourcing Stability Programs

Strategies for success

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STABILITY STUDIES ARE A CRITICAL PART of the drug development process and are essential for regulatory approval. Stability studies are required at all phases of the drug development life cycle. They establish the groundwork for understanding if the drug candidate is viable. Will the dose range and the formulation prove to be sufficiently robust to support the candidate's safety and efficacy? The information gained from these stability studies will help the pharmaceutical company determine and drive the drug development process. Decisions regarding the safe dosing range, excipients and active pharmaceutical ingredient (API) compatibility, formulation considerations, requirements essential for regulatory approval, expiration dating and quality control, are all supported by stability studies.

Stability studies are carried out at all phases for different reasons. These studies begin with preclinical stability to support animal toxicology. In Phase I, studies are used to establish drug/excipient compatibility, to assist in formulation development and ensure the stability of the API as formulated in the Clinical Trial Material (CTM). Data from accelerated/stressed conditions provide important information that is used to support early specifications. In Phase II and III, stability studies are conducted on the drug substance, and drug product and comparators during clinical trials. Later development stability programs form the basis for understanding degradation kinetics

and therefore provide the scientific rationale for the final specifications and shelf-life. Most importantly, stability studies are performed on manufacturing scale-up and/or process validation batches, and registration batches in final formulation and packaging for New Drug Application (NDA) filings. For Phase IV, marketed product stability studies are conducted to ensure commercial Quality Control. Also, Scale-Up and Post Approval Changes (SUPAC) and Product Life Cycle Management (PLCM) stability studies are used to support changes in the existing process and new dosage forms, delivery systems, and changes in packaging.

The increasing industry trend has been to outsource stability studies to contract research organizations (CROs). This is done primarily in an effort to reduce the cost of owning and maintaining the large operations necessary to drive the drug development process. There are certain advantages the pharmaceutical company can expect by forming a partnership with

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such firms to help drive their drug candidate. Contractor operations are dedicated in expertise, experience and infrastructure to carry out these studies efficiently and in full compliance with current regulations. There are many concerns in setting up and carrying out stability studies successfully and contracting with a reputable CRO will help the innovator navigate these challenges successfully. The following article discusses many factors for consideration in giving the overall picture of the process. These necessary considerations significantly reduce or eliminate risks of non compliance and invalid studies. Through the optimal choice of a contract supplier and careful planning for contingencies before and during the stability study, a successful outcome should be expected.

Decision to Outsource

The decision to outsource starts with a

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company's evaluation of its own current resources. The company management should ask if they have qualified and sufficient staff. Is there sufficient physical capital in stability storage capacity and/or analytical equipment, laboratory facilities and laboratory support? Stability studies demand access to unique instrumentation for analytical work. The equipment and capacity to store samples, maintain the chambers and monitor stability conditions require significant resources to manage and maintain. In addition it is necessary to have specialist expertise to conduct these

studies, evaluate results and comply with quality regulations. All of these aspects can be found in a good partnering CRO.

The process requires a number of coordinated departments from shipping and storage, characterization, formulation, analytical development, quality control, quality assurance and document control. For a virtual company, most often, none of these resources are available and are prohibitively expensive to set up, especially when the range of drug products ready for final development is small. Mid-sized to large companies are confronted with limited analytical resources for multiple projects in their pipeline. These constraints can be relieved by outsourcing some projects. This leaves scientific staff and analytical equipment free to be focused on other critical projects. To ensure success, choosing the right vendor is of paramount importance

Vendor Selection Process

Once the decision to outsource has been made, selection of the appropriate vendor to achieve the drug product lifecycle milestones is vital for success. The first factor for consideration is to understand the capacity of the outsourcing provider. As an example, the needs of the project must be clearly understood by both the company and the service provider. The product owner must understand whether the outsource provider is sufficiently capable and diversified to be able to give the services required. This would be true for all phases and types of stability studies.

Along with services provided, a company interested in outsourcing stability studies should ensure that the vendor personnel have the education, training and experience to work with their drug product. An ongoing training program is essential to retain the knowledge base and ensure that the technical aspects of the analytical testing are performed with a high level of competence.

It is of vital concern that the CRO provides a quality service according to guidelines stipulated by regulatory bodies. The CRO must have a well-documented quality system in place that is rigidly adhered to and involves QA

authority as an unbiased operation. The history of its FDA compliance record, including 483's and inspection history, should be requested and then reviewed for any significant findings. Experience with filings and responding to agency queries throughout the development

process (IND through NDA) is a significant advantage.

The sponsor needs to ensure that the stability conditions and capacity are available for their study. Concerning the stability sample storage, stability chambers must be monitored per regulations,

with back-up systems in place in the event of a power failure or other disaster. Excursions from acceptable ranges in storage conditions should automatically notify the stability chamber engineering staff. The stability chamber engineering team should be on call 24 hours a day, seven days a week to respond to an

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excursion. Both primary and secondary monitoring of storage conditions should be in place so that there are no gaps in stability storage data.

The customer should verify that the service provider has sufficient analytical instrumentation available. The quantity, quality and age of analytical equipment should be evaluated. The equipment should be in excellent working order and maintained within a regular service program. For samples that require specialized testing equipment, discussions should be made as to whether the equipment is available or can be obtained and brought into compliance in a timely fashion.

Cost is another important factor driving the decision to outsource. When comparing quotations from one vendor to another, it is essential that the scope of work being quoted is consistent. A quotation that is considerably higher or lower than other quotes should be carefully scrutinized as the scope of the project may have been ambiguous or misinterpreted. When comparing pricing from one company to another, one should also consider the experience of the company and its quality systems. While a lower cost service is attractive, it should not be the primary factor in choosing a service provider. You may encounter many more costly problems by using a provider that is "bargain basement." This often means that quality and integrity of the study

may be compromised. This inherently could invalidate a study and cost more time and money than if a quality organization were engaged in the first place.

Lastly, past experience with a provider, either directly, or through a reliable contact, is invaluable in the decision-making process. By performing a thorough evaluation using all the information available, a company should be able to make an informed decision in choosing the right service provider. A summary of the Critical Factors to Assess for a Contract Laboratory performing Stability Studies is found in Table 1. Once a CRO has been chosen, specific stability parameters need to be considered in advance.

Table 1: Critical Factors to assess for a contract laboratory performing stability studies

- Laboratory experience – GMP/GLP
- Laboratory equipment – quantity and quality
- Sufficient stability storage capacity
- Comprehensive calibration procedures
- Project director's technical expertise
- Thorough laboratory analyst training program and experienced analysts
- Method validation and method transfer policies
- QA support systems and thorough SOP system
- FDA inspection history and your audit results
- Sample handling system that ensures chain of custody
- Compliant laboratory investigation procedure
- Technical review and QA review procedure for reported analytical results
- Document/data control and storage
- Operational Excellence Program – Continuous Improvement
- Regular customer feedback solicited
- CAPA system
- Cost of Study

Stability Project Start-up

The first step in the project start-up is to establish expectations. The major milestones for the project — such as availability of the samples, filing and manufacturing deadlines, clinical trial start dates and other key events — should be shared so that the project plans can be tailored to meet these deadlines. The testing start window and the turnaround time for data reporting should be established early in the process. Additionally, a quality agreement between client and contractor may be put in place to assist in clarifying expectations.

Concerning the analytical test methods, discussions concerning the status of the methods should be made to determine whether a method transfer, a method qualification for a USP method or method development and/or method validation is required. These should follow the appropriate regulatory guidelines and are determined by the development phase of the drug product. Validated methods are required for the final phases of the drug product life cycle.

The next step requires a stability protocol to be written and approved by both parties where parameters for testing are described in detail. The protocol is designed to assess the stability characteristics of the drug product. The results of the stability study are used in determining appropriate storage conditions and expiration dates. The protocol should minimally include: (1) the sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability, (2) storage conditions for samples that are to be tested, (3) specific test methods that are robust and meaningful, (4) the drug product stored in the same container-closure system as the marketed drug product, and (5) for product that is reconstituted, testing of the drug product at the time of reconstitution and after appropriate time intervals after reconstitution, according to the labeling. A summary of the Key Sections of a Stability Protocol is found in Table 2. If specifications are unknown, validation results can be used to assist in determination of specifications. Data reporting may be generated through a Certificate of Analysis (CoA), summary trend tables, and/or direct entry into Laboratory Information Management System (LIMS). Thorough initial testing of the product is essential to establish a good baseline for future

Table 2: Key sections of a stability protocol

- Project scope
- Quality systems to be utilized
- Applicable regularity requirements
- Sample and standard description and handling
- Shipping conditions for temperature or light or moisture sensitive drugs
- Safety information (MSDS)
- Test methods
- Data reporting requirements
- Acceptance criteria or specifications
- Client notification limits
- Stability sample pull schedule storage conditions and quantities
- Initial testing requirements
- Testing windows
- Third party testing information (if applicable)
- Final report requirements

trending. Once the stability set-up is in place, monitoring the study and vendor metrics is essential to keeping the stability project on track.

Monitoring the Study and Vendor Metrics

As stability studies are entirely time dependent and often extend two to five years, it is crucial that they are well monitored to prevent time point data — or indeed an entire study — from becoming invalidated due to negligence and errors. A variety of tools are used to ensure that monitoring is maintained and the study remains viable. A communication plan with regular teleconferences and emails should be in place. The plan can depend on a risk assessment and should be implemented in the stability start-up phase. The aim of such a plan is to ensure that all factors, contingencies and issues pertaining to a study are communicated and accounted for.

Additionally, there needs to be an escalation communication plan for urgent matters that arise, such as out-of-specification, out-of-trend situations or unusual observations. These situations need to be dealt with immediately to remain within project timelines and respond to situations that may require a shift in pathway to achieve the project aims.

As data are generated, there need to be mechanisms for trending to ensure that results are within acceptable trend variations. As the time points progress, there may be need for method or specification changes if the drug material behaves in an unexpected fashion. This can all be achieved by having change control procedures in place.

Another important aspect of ensuring a successful stability program is to develop metrics to evaluate the vendor's performance. Some areas that one can evaluate are testing within the test window, measurement of on-time delivery of data and reports, "right the first time" on report accuracy, and number of

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investigations that are determined to have analyst error as the root cause.

Some contract labs have their own internal metrics that are used to track their own performance. By developing a culture of continuous improvement through an operational excellence program, a CRO can differentiate its performance from competitors. These programs often align companies that have common continuous improvement cultures.

As part of a vendor compliance program, it is recommended that the outsourcing client perform regular audits of the testing facility. The contract lab should have a timely response to the audit findings and develop an implementation plan for remediation of the audit findings. In this way, issues are quickly resolved that would otherwise impede timely progress and corrective action prevention action plans (CAPA) can be enforced to prevent reoccurrence.

Stability studies present many challenges, as they are costly, time- and resource-consuming and subject to significant regulatory scrutiny. The demands for quality and timeliness are pivotal to the success of the project. It is clear that the relationship between client and contractor must be strong and dedicated as they work together to address the many issues that occur during the execution of a stability program. Towards this aim, CRO companies concentrate their business to meet the needs of their clients by providing well-coordinated resources of well-maintained and reliable equipment, trained and qualified personnel and systems for quality and timely execution. Additionally the service provider should have an understanding of project requirements, plan for contingencies and monitor projects for excellence and efficiencies. Ultimately, by developing a strong technical and business relationship, there is a synergistic effect where both the client and contract lab can benefit from a successful stability program. ■

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