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Pharma Expectations in Outsourcing Stability Programs

Stability testing is an important aspect of any drug development project, and it is a requirement for manufacturing approved drug products. The information from such development studies is used to determine acceptable shelf life, proper storage conditions, and suitable packaging. Essential information regarding product quality over its useful lifetime is gathered about potency, impurity levels and integrity of the drug delivery scheme (oral or otherwise).

Conducting a stability testing program is not a trivial task. These studies can last from one to five years. Considering that a typical stability program may include three different manufactured lots, one to three packaging configurations, and three storage conditions, a large amount of data will be generated during the course of a stability study under the auspices of Current Good Manufacturing Practices (cGMP).

Pharmaceutical companies frequently contract these programs to an outside testing facility because they don't have the resources in house. Their expectations of the contract laboratory are high. There is substantial financial risk in placing such a long-term study with an outside organization that might not perform. Mishandling a project one, two or three years into a study is very costly in both money and time. A delay can cost a pharmaceutical company millions of dollars.

What does a sponsor company look for to ensure that their stability programs will be executed correctly? Sponsors are looking for laboratories able to maintain sample integrity, analyze samples in compliance with cGMP requirements, and provide quality assurance services. Intertwined with these three primary areas of interest is a list of intangible assets. The sponsor has the responsibility of assuring that their studies are conducted in a compliant fashion. To make this determination, the sponsor company will inspect the Contract Research Organization (CRO).

Sample Integrity

From the time a sample enters the building to its final disposition, sample integrity must be maintained. Sample integrity includes correct labeling of identity (drug name, lot number, etc.). The sample and its package should not be compromised in any fashion throughout the study. Auditors will examine sample storage areas looking for organization, adequate segregation of samples, security, and documentation of sample custody.

A well-organized, clean space will ensure adequate segregation. Areas littered with boxes, bottles, paperwork and other paraphernalia leave the auditor doubting the lab's ability to keep track of samples. Auditors are concerned that their samples may get placed with samples from other sponsors or that samples from different studies will be mixed. Well-labeled bins or well-marked shelves with dividers will ensure study samples are separated and that tested and untested samples are separated.

Clients expect that samples will be stored in a secure location, in the recommended conditions, and that storage is documented. Preferably, access to the samples should be limited. Clients want to be assured that their samples aren't lying around in the open. Sample custody and the inventory of every tablet is crucial. Keeping tested samples segregated from untested samples gives added assurance that samples are well maintained. Sponsors will look for validated sample tracking systems. LIMS systems are useful in providing a tracking function. If a LIMS system is not implemented, then a paper system must ensure that the samples can be tracked throughout the life cycle and that all aspects of their handling and environment are well documented.

Laboratory

According to cGMPs, samples must be analyzed using validated methods, tested on qualified instruments, assayed by trained scientists, with documentation to support not only the results but all activities. In addition, all work must be reviewed appropriately. Sponsors will look for systems and processes that ensure these requirements are met. A review of the CRO Standard Operating Procedures (SOPs) will provide insight into these processes.

Auditors will look for validation reports or certification approving the CRO to run methods. They will examine instrument records thoroughly. The scrutiny entails examining installation, operational and performance qualifications; maintenance and repair records; and use logs. They will also discuss training programs at length and look at training documentation. Of course, they will read all SOPs to be sure they are adequate for all processes.

Training is of particular interest. The cGMPs require that an adequate number of qualified persons be involved with the study and that these persons have the appropriate education, experience and training. Training programs should include initial training from the scientist's employment date, ongoing training, and regulatory training. Regulatory training must be provided on an annual basis.

Documentation practices must be sound. SOPs must be accessible to laboratory staff. Sponsors do not seem to have specific preferences about documentation format (notebooks vs.

forms, for example), but are simply concerned that all information necessary to assure the integrity of the data is captured. Data must be secure and not in danger of being lost, altered or destroyed. Prevention of fraudulent practices must be evident. Document control is of great interest to sponsors. Can they be assured that the most current version of SOPs and methods are being used? They also want to see the process for making changes to documents. Is this done in a controlled fashion?

The SOP most frequently requested by cGMP auditors is the procedure for out-of-specification (OOS) investigations. This SOP is always highly scrutinized and sponsors examine the process closely. The Barr decision of 1993 mandated that investigation of results that fall out of specification be documented thoroughly. The analyst must determine with the supervisor whether a laboratory error occurred. Any additional data generation must be planned, documented and approved prior to execution. Sponsors seek comfort in knowing that aberrant results are dealt with in technically sound fashion and that corrective or preventive actions are put in place when necessary.

Quality Assurance

Key to every laboratory is the regulatory oversight function of a Quality Assurance Unit. QAU serves the laboratory by auditing processes, data, reports and protocols. In addition, QAU must maintain a working knowledge of the regulations and ensure that laboratory operations are in compliance. Sponsors will look for a QAU that is independent of the laboratory and reports directly to management. They will look for sound auditing and reporting practices. Sponsors also expect that deviation trending, investigations and follow up on corrective actions when necessary are part of the process.

Currently, of foremost interest is compliance to 21CFR Part 11, which covers use of, and requirements for, electronic records and electronic signatures. The industry is focusing attention and resources on bringing operations into compliance; however, compliant applications are not universally available at this time. In these cases, sponsors look for a gap analysis document showing a proactive approach to meeting this requirement. The sponsor will want to know where deficiencies exist, how deficiencies are handled currently, and the plan to meet compliance. Computerized systems are an integral part of most operations, and regulations require validation of these systems. The sponsor has a vested interest that these systems perform adequately, so software validation documentation is provided for sponsor examination.

An exemplary record with the FDA provides an additional boost in the confidence level of pharmaceutical industry representatives, and auditors are extremely interested in the results of any completed FDA inspections. Laboratory systems that can withstand FDA scrutiny are sound and are a good indicator of future performance. Results of these inspections, as well as the laboratory response, are examined.

Intangible Qualities

Sponsors need assurance that laboratories are providing services in compliance with the Good Manufacturing Practices. It's a given that most contract organizations are going to operate with a complete and detailed set of SOPs based upon the regulations. (The regulations do allow for a wide range of interpretations and philosophies.) Auditors collect information regarding the systems the laboratory follows. However, sponsors are also looking for other intangible qualities that often can be the deciding factor among competing laboratories. These are responsiveness, trust, cost and scientific expertise.

Everyone will agree that good communication is necessary for the success of any contract relationship. This particular topic arises in any discussion about outsourcing; however, its importance should not be trivialized. Sponsors look for those who can communicate, and the communication process begins with the first contact. To ensure success, both parties should state their expectations up front. Establishing the rules in a clear, concise manner at the beginning prevents misunderstandings and frustrations. Decisions about data presentation and report format made prior to the start of the study also ensure seamless flow of work.

Because the sponsor project scientists rely on the laboratory to complete their projects, they expect the laboratory to provide timely responses to their inquiries. Sponsors need to know that their project, their question, their concern is the laboratory's top priority, and the contract laboratory scientists believe the consideration should be returned!

Showing a propensity to respond in a timely fashion will also set the tone for data delivery. Sponsors want to know how quickly or how slowly their data will be available. The window to complete testing can be tight. Sponsors expect that timelines will be met, particularly with stability samples for which the analysis schedule is preset. Of course, when schedule adjustments must be made, immediate notification is expected. Sponsors appreciate honesty. They would rather be told a realistic timeline instead of one the client might expect but the laboratory can't deliver.

Sponsors appreciate confidentiality and professional treatment of their studies. They also appreciate the scientific expertise and insights provided with the data. A good partnership with a CRO can actually enhance the project for the sponsor, particularly for smaller or "virtual" pharma companies. Sponsors who are able to talk directly with the scientific staff and get immediate information regarding their study feel more confident about the attention given to their work.

Essentially, the laboratory should be able to function as if it were just down the hall from the sponsor. In reality, such a geographic relationship is seldom the case. Thousands of miles may separate the two; however, in today's age of fax, Internet access, Webcast capability, video conferencing and even teleconferencing, geographic distance is less important. Still, some sponsors put merit on having a laboratory nearby, and close proximity can enable same-day delivery of samples or data. If a problem arises, the sponsor can access the laboratory easily. Some sponsors feel an added comfort level with a laboratory within driving distance.

When about to begin a stability program, whether a sponsor elects to outsource or keep it in house, the facility must have a secure, controlled

environment that will maintain sample integrity. The facility should have laboratory procedures that provide training, qualified instruments, validated methods, and controlled documentation. The quality assurance unit must have intact systems. Above all, the sponsor must feel confident that the laboratory can execute the protocol in a timely fashion, in line with the regulations, and that the final data package provided will withstand FDA scrutiny. After all, the bottom line for the sponsor is to get FDA approval for their product.

Typical Stability Protocol in Support of a New Drug Application

All stability studies are protocol-driven. The protocol outlines all aspects of the study and details the data that is expected. The essential parts of a protocol are listed below.

- Purpose
- Sample Description: lot numbers, drug substance information, dosage form, batch size
- Package Description: package material, suppliers, lot numbers, size, type
- Tests to Perform
- Stability Data Acceptance Criteria
- Test Schedule
- Data Analysis Methods
- Report Requirements and Format
- Location of Data/Reports
- Additional Comments
- Attachments
- Signatures

Information Sources

1. *Food and Drug Administration, www.fda.gov*
2. *Center for Drug Evaluation and Research, www.fda.gov/cder*
3. *United States Pharmacopeia*

T1. A typical test schedule or stability grid. For **each lot** of drug product, an appropriate amount of units will be placed in the chambers to allow for all required testing. The settings for the environmental chambers are shown in the left-hand column. The testing will begin at time = 0 (also known as the initial time point). Enough samples will be removed from the chambers at the given elapsed time to complete the prescribed testing. In the grid below, an "X" indicates that samples are pulled and tested.

	Time Points									
Conditions	**Initial**	**6 wks.**	**3 mo.**	**6 mo.**	**9 mo.**	**12 mo.**	**18 mo.**	**24 mo.**	**36 mo.**	**48 mo.**
25°C/60%RH			X	X	X	X	X	X	X	X
30°C/60%RH		X	X	X		X				
40°C/75%RH	X	X	X	X		X				
5°C		X	X	X	X	X	X	X	X	X