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WHITE PAPER

Stability Study Design: Pharmaceutical Stability and Data Evaluation

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Stability Study Design

Pharmaceutical Stability and Data Evaluation

The pharmaceutical development process is a complex, multi-phase journey that transforms a drug idea into a marketable product. This process typically includes several key phases: drug discovery, preclinical development, clinical trials (Phases I, II, and III), and regulatory approval, followed by post-marketing surveillance. Integral to each phase of development is the collection of stability data on the active Drug Substance and the final Drug Product. Stability testing demonstrates that the product maintains its quality throughout its shelf life and helps identify potential risks associated with the product's degradation. By identifying degradation pathways and their kinetics early in development, pharmaceutical companies can develop strategies to mitigate these risks, reducing the risk of adverse events and recalls.

Well-designed studies can also provide a cost-effective way to guide development while maintaining product quality. By understanding the product's stability, pharmaceutical companies can identify appropriate packaging and storage conditions, reducing the likelihood of product degradation and the need to discard viable products. Depending on the number of batches, study duration, packaging components, dose strengths, and final dosage forms, stability studies can be lean or extensive depending on the amount of data required to support development needs. Understanding the stability requirements for each phase of development will keep costs down and will also increase the probability of a successful drug development campaign.

Stability Considerations for Early Phase Drug Development

The Drug Substance development process begins with the identification of potential or lead drug candidates. As therapeutic targets are confirmed, and lead optimization efforts are proven successful, preclinical development campaigns begin. Companies then assess the active Drug Substance for safety and biological activity through toxicological, in vitro, and in vivo studies. The Drug Substance batches used for such purposes are most often small in scale and manufactured with a synthetic process that is not yet optimized. However, even at this early stage, it is recommended that at least one batch of Drug Substance which is representative of the current manufacturing process be placed on stability as soon as possible after candidate selection. Though the batch may be rudimentary with respect to process development and scale, these studies are critical as they can provide early insights into the stability and degradation pathways of the drug.

Though early phase development is outside the scope of the ICH Q1A(R2) guidance and only a limited number of batches are likely available, it is recommended that the procedures and study design be consistent with ICH requirements. Using a risked-based approach, companies can formulate a development strategy that minimizes the amount of drug substance required to support the setting of a preliminary re-test period. These data are key to enabling initial Investigational New Drug (IND) or Investigational Medicinal Product Dossier (IMPD) applications on an accelerated development timeline.

Regulatory Compliance

In both the US and European countries, the FDA (CGMP for Phase 1 Investigational New Drugs) and EMA (requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials) guidances recommend that at Phase 1 for an investigational drug, a stability study using representative samples should be initiated to monitor the stability and quality of the drug during clinical trials. This practice not only ensures patient safety, but the data acquired from stability testing will provide evidence of the continued quality of the active Drug Substance or final Drug Product over time.

The EMA recommends when filing an Investigational Medicinal Product Dossier (IMPD) that stability studies begin prior to the start of the clinical trial, with a minimum of 3 months stability data having been collected at both accelerated and long-term storage conditions. The stability data should be accompanied by a shelf-life statement supporting the assigned product expiration period that will be used throughout the clinical trial duration. Recent experience indicates that the EMA will frequently accept data from a welldesigned Accelerated Stability Assessment Program (ASAP) study to support the setting of an initial Drug Product expiry period. For an IND filing, the FDA does not require stability results or a shelf-life statement on product labels, however these data should be available if requested.

In addition to the requirements by the FDA and EMA, other agencies such as the Japanese Ministry of Health or the World Health Organization provide specific guidelines for pharmaceutical stability testing in other regions around the globe. Therefore, companies are urged to pay close attention to the regulatory requirements for each region and climatic zone, as each country is responsible for setting their own stability storage requirements. Comparing the requirements set forth by each agency, small differences exist for acceptance criteria, data analysis requirements, and documentation standards. However, all agencies are required to align with ICH stability requirements.

Stability Protocol Design

Stability studies ensure that medicinal products maintain their safety, efficacy, and quality throughout shelf life. The creation of a GMP-compliant stability protocol is a prerequisite for these tests, serving as a blueprint that outlines the testing framework. The stability protocol is more than just a document outlining the testing and specification requirement; it's a strategic tool that ensures alignment across all stakeholders and development partners, while facilitating a seamless process that meets stringent regulatory requirements in the context of the sponsor's overall development strategy.

A stability protocol should also include a sampling plan detailing the number samples or containers that must be pulled from the stability chamber at each time point, as well as the number of extra samples placed in each chamber in case a retest is required. The sampling plan should include instructions for how the samples are stored after removal from the stability chamber prior to the initiation of testing. Protocols should provide clear instructions and criteria for data reporting, which are in alignment with the analytical procedures used in the evaluations of each quality attribute. And lastly, stability protocols and/or site-specific Standard Operating Procedures (SOPs) should contain detailed information regarding the stability specification criteria that have been assigned to each quality attribute.

Scope:

Identify the products and stability parameters to monitor, such as pH, appearance, or active ingredient content.

Storage conditions:

Consider the intended use of the drug as well as any climatic, regional, distribution, or marketing conditions for the product when determining the appropriate storage conditions.

Analytical Procedures:

Consider the suitability of each analytical method for the testing of each specific drug or drug product and validation or verification requirements must be met to ensure accuracy and reliability of test results.

Testing frequency:

Using a risk-based approach, determine how often the stability samples shall be tested to demonstrate stability; the testing frequency is typically determined by the Critical Quality Attributes (CQA) of the specific drug and in conjunction withintended shelf life.

Batch selection:

Select batches that best represent the current manufacturing process and when possible, consider that stability data from multiple batches can increase the statistical power of your study outcomes.

Acceptance criteria:

Establish acceptance criteria for the stability parameters.

Packaging:

Consider how the packaging components may affect orinfluence the stability of the pharmaceutical product (or vice-versa).

Container orientation:

Consider how the product's stability is affected by the orientation of the container during storage.

Study design:

Whether to use full and reduced study designs to collect comprehensive data.

A stability protocol can be thought of as a network of interdependent documents that are used to build a framework for the testing of stability samples. Having cohesion amongst the contents of the stability protocol, analytical procedures, and SOPs is important for consistency and efficiency throughout the study period. Additionally, having alignment across this network is beneficial in the event that any data points are reported as Out of Trend (OOT) or Out of Specification (OOS). OOT and OOS results are not uncommon in stability studies and most often, confirmed OOT or OOS results require investigative testing. Such testing requires a tactful and timely response to ensure that the data gathered throughout the investigation is representative of the original OOT or OOS result. All parties should agree prior to the initiation of the stability study on what actions should be taken to properly mitigate such matters.

Analytical Procedures

Another factor that must be considered early when designing effective stability programs is the development of phase-appropriate analytical methods. Depending on the phase of development the stability study is supporting, the rigor to which each method is developed and validated can be different. For example, the validation requirements for early phase analytical procedures are quite limited, whereas the validation standards for methods supporting phase 3 or registration studies are more comprehensive. For most companies, early stages of product development will consist of the manufacture of a limited number of batches, often on a small scale, using a drug substance synthetic process that isn't yet optimized. Thus, knowledge of likely impurities (synthetic impurities, degradation products, or those arising from the raw materials) may be limited. Understanding these limitations and employing a phase appropriate strategy that scales method development, optimization, and validation activities to suit the needs of each phase, will help avoid high costs and unnecessary rework downstream.

In early phase development, the testing of the drug substance is the primary focus. Doing so will confirm the potency and safety of the drug going into the clinic. Therefore, the two most important drug substance methods that should be established initially are methods to assess assay and impurities content. Demonstrating the specificity, accuracy, precision, and quantitation limits of each method satisfies the validation requirements for early phase analytical procedures. Additional validation activities may be performed but are not necessary. Each method should be capable of separating the active component from impurities, either those synthetic in origin or those arising from the raw materials and intermediates. Stress studies (or forced degradation studies) showing the stability indicating power of each method should be performed to demonstrate the separation of degradation products as well.

Once the stability indicating ability of the initial analytical methods has been confirmed and the stability studies have begun. Stability data will be collected from samples of pharmaceutical goods that have been subjected to environmental stressors such as temperature, humidity, and light. The stability study will continue throughout Phase I and span the length of the proposed clinical dosing period. Evaluations made from the stability data at both long term and accelerated storage conditions are used to predict long-term performance of the active Drug Substance and the final Drug Product. These data are used to estimate the retest period of the Drug Substance or the shelf life of the final Drug Product under specific storage conditions.

Phase 2

Development

Stability Design Considerations

For Phase 2 clinical trials, an evaluation of the stability data detailing overall product stability should be submitted. In accordance with the U.S. FDA Guidance for Industry INDs for Phase 2 and Phase 3 Chemistry, Manufacturing and Controls Information, this evaluation should include specific study information regarding study length, storage conditions, acceptance criteria, time points, and detailed information on the analytical procedures. When possible, it is advised that the study length cover the clinical dosing period to avoid material expiration. However, alternative strategies that rely on re-supply of materials to the clinic prior to expiration, can also be employed to effectively manage clinical drug product inventory for longer clinical studies.

By Phase 2 most drug companies have optimized their API manufacturing process to a point where known impurities have been identified, qualified in a toxicology study, and reference materials of these compounds are available. It is also important to have a good understanding of the potential degradation products that are most likely to manifest on stability and ensure that the analytical procedures are suitable for the analysis of the stability samples. ICH Q1A(R2), EMA CPMP/QWP/122/02, and FDA guidelines recommend that for substances not covered by official monographs, stability indicating quantitative assay procedures be established.

To demonstrate the stability indicating power of any analytical procedure, method developers are encouraged to perform forced degradation studies. This is the process whereby drugs are commonly exposed to extreme conditions of photolytic, oxidative, hydrolytic, acidic, basic, and thermal stress with the intent to degrade the drug to elicit primary degradation products. This allows analysts to confirm that the analytical procedures can identify and accurately measure the compounds most likely to appear during long-term stability.

For most companies the end of Phase 2 is marked by some key milestones. The Drug Substance manufacturing process is validated and consistent. The final Drug Product form, dosage strengths, and degradation pathways are likely well understood. The analytical methods for both Drug Substance and Drug Product are validated and several months, if not years, of stability data have been acquired. As companies move into Phase 3, the primary focus shifts from supporting the investigational (clinical) Drug Product to generating stability data to support the proposed commercial product packaging presentation.

Phase 3

Registration and Post-Approval

Stability Design Considerations

Phase 3 stability studies to support the investigational (clinical) drug product are often used as the registration stability studies, though studies designed specifically for regulatory submissions can be performed. Once Phase 3 development has been begun, stability protocols must be compliant with all ICH Q1A guidelines as the data gatheredfrom these stability programs may be necessary to support registration applications.

Long-term and accelerated stability studies in Phase 3 should be carried out on the Drug Substance and the Drug Product in a container closure system that represents the final container closure system planned for commercial supply. Formalized stress studies, if not carried out earlier, must be completed during Phase 3. This should include photostability, shipping, and temperature excursion studies designed to challenge the product in the final packaging configuration and to confirm stability during transit and storage.

Stability Analysis and Shelf-Life Management in Pharmaceutical Products

Shelf-Life Determination

As previously discussed, the collection of stability data is inherent to every step of the drug development process. For most companies, these data are a critical source of product knowledge and can be leveraged for many different purposes. Data gathered throughout stability testing are used to establish product retest and shelf-life periods.

Retest dating

Retest dating is the time in which a pharmaceutical material is deemed suitable for use before it must be reexamined, to once again demonstrate suitability of use. This applies to materials where minor changes over time are acceptable and can be addressed within the manufacturing process to maintain material quality. Materials such as Regulatory Starting Materials, Drug Substances, Active Pharmaceutical Ingredients, and Drug Product Intermediates may be given extended retest intervals based on stability performance and overall safety risk.

Shelf-Life (or Expiry) Period

Shelf-Life (or Expiry) Period refers to the period during which a drug product has been demonstrated to remain within its specified quality parameters under defined storage conditions. The Shelf-life is estimated based on the collection of stability data for a pharmaceutical product in the final dosage form. It may also be the point at which no further stability data is available and shelf-life extensions are no longer feasible based on available data. During this timeframe, the product's safety and efficacy should be preserved. ICH and EMA regulations mandate continuous collection of stability data throughout the shelf-life to ensure that the product remains within quality limits and to provide scientific justification for shelf-life estimations.

Expiration (or Expiry) Date

Expiration (or Expiry) Date is the date calculated by applying the approved shelf-life to the Date of Manufacture (DOM) for each batch of drug product. It denotes the date beyond which the drug product batch should no longer be used.

Shelf-Life and Retest Strategy

Initially, in early phase development, shelf-life intervals are often short as only a limited amount of stability data is available. Yet with only a small amount of data, even data from a single batch, an extension of the shelf-life by several months can be supported. While compliance to the ICH stability guidelines is limited to commercial materials, during development, ICH guidelines can be used as an initial basis for justifying a retest or expiry period. However, less conservative approaches can often be supported in conjunction with a commitment to continue to collect concurrent stability data.

Regulatory guidelines vary by region, but most countries allow for extensions of shelf life in cases where minimal variability and no obvious data trends exist. For example, extensions up to twice (2X) the duration of current stability data under long-term or accelerated conditions (maximum of 12 months beyond) are allowed per ICH Q1E for products stored at room temperature. Additionally, for products requiring cold storage, a permitted extension of up to 6 months beyond the current data is justified.

For products requiring refrigeration or freezing, extensions can be up to one and a half times (1.5X) the current data, not exceeding 6 months past the current point.

European regulations align closely with these allowances, though EMA 545525 provides a notable exception, allowing up to a fourfold (4X) extension of accelerated stability data (maximum of 12 months beyond). Also as mentioned above, the EMA will frequently accept data from a well-designed ASAP study to support the setting of an initial Drug Product expiry period. This can be particularly advantageous

for companies establishing initial shelf-life intervals with limited stability data. Significant time constraints associated with release testing, packaging, shipment, customs clearance (if necessary), and clinical dosing can be incurred. Therefore, it is beneficial to take advantage of these allowances to minimize the risk of product loss. Furthermore, the setting of an initial shelf life is required by the EMA as all product labels must contain the expiration date for any pharmaceutical product used in Europe.

Once an initial retest or product shelf life has been established, the use period can be continually extended based on the collection of additional stability data, assuming no significant data trends are observed. Typically, once 3-6 months of stability data are available at long term and accelerated storage conditions, companies can begin analyzing the data for trends. Often this is the point when enough data points exist to for a regression analysis to be statistically significant, thereby enabling preliminary, data-based estimations of shelf life. In cases where no obvious data trends exist, no statistical analysis of the data set is required to support shelf-life estimations and extensions.

When necessary to perform linear regression analysis of a stability data set, the use of statistical software platforms such as JMP, Minitab, Stata, or Alteryx can be vastly beneficial in the prediction of product shelf life. Linear regression analysis allows sponsors to estimate the future point in time when a product may fail to meet specification requirements. Such analyses can be performed using data from a single batch or multiple batches, though the use of data from multiple batches is the best way to increase the statistical power of a data set. Pooling data from multiple batches, where statistically justified, can enhance the statistical accuracy of the estimated shelf-life intervals.

Batch pooling also allows sponsors to compare the similarity of data points collected from multiple batches simultaneously to determine with a high degree of confidence if each batch will maintain acceptable quality throughout the proposed shelf-life period. In cases where the regression analysis estimates that the shelf-life for all batches meet or exceed the current shelf life for all quality attributes, the data is considered supportive of the shelflife proposal. In such cases, all batches are assigned the same shelf-life interval. If, however, it is determined that the shelf-life estimate for any batch is found less than the current shelf-life period, it may be necessary to establish batch specific shelf-life periods or shorten the overall shelf-life of the product to account for this.

Setting an appropriate shelf-life requires consideration of numerous factors, including stability data, observed trends, product demand, manufacturing capabilities, and costs. A systematic approach to stability analysis and strategic planning ensures efficient use of materials and scientifically justified shelf-life intervals.

Conclusion

In summary, the stability testing of pharmaceutical products plays a crucial role in ensuring that drug products maintain their safety, quality, and efficacy throughout development and well after commercialization. Stability testing is integral at every phase—from early drug discovery through clinical trials and into post-marketing surveillance. Early-phase testing offers valuable insights into degradation pathways, while Phase 2 and 3 studies provide more robust stability data to support regulatory submissions. Compliance with regulatory agencies such as the FDA, EMA, and WHO is essential, as their guidelines dictate stability requirements, including storage conditions, batch testing, and data analysis. Well-designed stability protocols streamline product development by aligning manufacturing practices with analytical procedures, helping companies optimize storage conditions and predict shelf-life accurately. This approach minimizes risks associated with product degradation and ensures that drug products meet quality standards across global markets. Through continuous data collection and predictive analysis, companies can set appropriate shelf-life intervals, ensuring patient safety and regulatory compliance while efficiently managing production and costs.

ABOUT

Syner-G

Syner-G offers solutions in stability study design, data evaluation, and shelf- life determination. Our services are grounded in deep regulatory expertise and scientific rigor, ensuring that our clients' stability protocols are not only compliant with global guidelines (FDA, EMA, ICH) but also strategically designed to optimize resources and timelines. From early- phase stability testing that provides critical degradation insights to the design and execution of registration stability studies that support regulatory submissions, Syner-G is equipped to guide clients through every step of the process.

Syner-G provides comprehensive services in product development, regulatory strategy and submissions, functional outsourcing, medical writing, and quality and compliance, all supported by program management and submission expertise. With an integrated approach, we guide biotech and pharmaceutical companies through developmental challenges and complex regulatory filings to achieve timely, high-quality submissions. As a trusted partner, we offer tailored technical and operational solutions across every phase of the drug development lifecycle to help clients

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