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White Paper

Taking Charge of your Stability Program

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Introduction

Conducting stability studies is a critical aspect of the drug development process, as the information gained determines key clinical development decisions and becomes an essential component of the submission package required by regulatory authorities globally. For any biological therapy, there is a set of attributes that is critical to maintaining the product's safety and efficacy; the purpose of stability studies is to analyze these attributes at predetermined timepoints during the study to understand how they may be impacted by storage in different environmental conditions. Through understanding the links between storage and product degradation that may give rise to loss of biological activity, possible toxicity or unwanted immunogenicity that pose potential risk to patient health, stability studies generate the data necessary to specify the storage conditions required to maintain product quality and safety and justify the shelf life and expiration dates for your biological product.

Stability Testing in Biologics

Development of biologics therapies is a challenging and lengthy process due to the complexity of manufacturing products such as monoclonal antibodies (mAbs) in biological systems. Amongst the global regulatory guidelines for product development are documents focused on determining product stability (International Committee for Harmonization (ICH) documents Q1A/B and Q5C) outline the expectations for drug developers to conduct stability studies to prove the product's long-term viability, safety, and efficacy, both on drug substance (DS) and drug product (DP). Hence some stability data is required to enter clinical trials, however throughout the life cycle, more detailed and long-term studies are needed to justify storage and shelf-life conditions in regulatory submissions for entry to market.

Planning: Considerations and Contingencies

Stability studies are complex, involving testing of DS and DP samples using a whole package of assays over long periods of time with consistency needed throughout the study duration and consequently, they require extensive planning and preparation. This ensures studies can begin in line with planned manufacturing commitments, and that the data generated is as meaningful and informative as possible. Proactively addressing the possible challenges helps ensure successful execution. Here are a few major planning considerations:

- What attributes of the product will be tested as part of the stability program? What analytical methods need to be developed?
- Do you have representative product material needed to establish product specific assays available and in sufficient quantity?
- Does the study align with the manufacturing schedule and sampling plan?
- What storage conditions will be included? Are stress studies required?
- Will you need to outsource part or all of the activities involved in the stability study? If so, then additional time may be needed to find and coordinate the study with your supplier

Complex molecules such as monoclonal antibodies (mAbs) have considerable potential for structural variability. Maintaining product quality requires careful process control and knowing the appropriate storage conditions that need to be determined through stability studies. Some well-established links between structural variability such as post-translational modifications (PTM), oxidation, deamidation events or increased aggregation and the risks to product efficacy, safety, and purity are summarized in **Figure 1**.

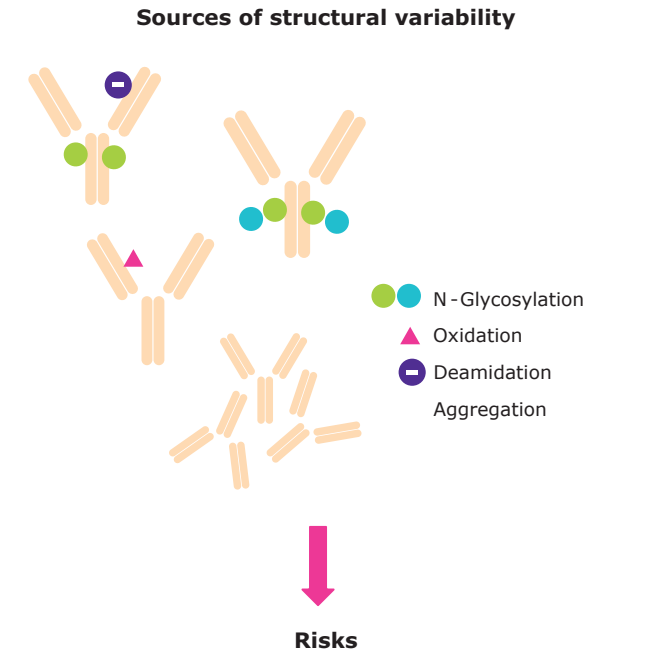

Figure 1: Sources of structural variability

Stability Testing Methods

Stability studies requires assay packages, ranging from compendial tests to complex methods used to assess levels of impurities, structural attributes such as post-translational modifications, as well as biological activities. Assay packages will be tailored based on knowledge of the product's molecular structure and anticipated mechanism of action (MOA). Primary concerns to consider prior to entering Phase 1 clinical trials is the assays that comprise the package and time required. In particular, the stability-indicating methods for several months' product stability are required. Custom methods are developed from scratch, which can be challenging and require more time than anticipated, so establishing a contingency plan that allows you to change strategies or technologies may be required. Other considerations include:

- Preparation needed in order to challenge stability indicating properties in the relevant assays, as methods need sufficient resolution to distinguish impurities and degradation products as they arise. This includes the generation of samples suitable to assess stability-indicating properties that are typically generated using stress studies or forced degradation studies, as recommended in regulations such as ICH Q1 R2.
- Planning to include sufficient time to assess performance of the assays. For initial early phase, GMP stability methods would be qualified. In later stages of development, you would need to fully validate them.
- Ensuring there is a sufficient supply of representative product samples (Reference standards), reflecting the manufacturing process used to prepare the batches to be assessed for stability, to develop and qualify/validate the custom assay methods required, as well as other critical biological reagents needed to support these assays. This level of planning helps avoid having to perform bridging studies which could complicate the interpretation of the stability study results.

Preparing essential documentation

Sampling Plan

After developing and locking down a process at a given scale, schedules are implemented to manufacture batches of DS and DP, which requires careful coordination between manufacturing and QC/analytical teams within your organization or, with your CMO partner. Creating a manufacturing sampling plan is necessary to capture all the details about the lot size (the number of vials/bags of material), which will determine the number of samples available for lot release, clinical/commercial use, and stability testing as well as sampling information (number of vials for testing, or retains), testing packages for the different samples and volumes needed for each assay). Hence, the establishment of the sampling plan is key to planning for the stability study, and coordination and alignment to the stability study protocol is required.

Stability Study Protocols

Likewise, a GMP stability protocol is critical to the success of the study since it outlines the conditions to be evaluated and the sampling plan, numbers of vials to be stored to enable the testing requirements at each timepoint (plus retains), details of the assays to be used as well as critical materials and reagents utilized in the study. It is important to allow sufficient time to prepare and perform the necessary reviews including QA oversight to ensure accuracy and clarity. If outsourcing the study then there may be additional coordination and time required to prepare, review, and approve for a GMP study ensuring all parties are clear on the study plan. Preparing the protocol well in advance of the planned study initiation helps ensure successful execution of the stability study.

Key decisions for planning and conducting stability studies

In addition to the practical considerations discussed above, there are other issues that can add complexity to conducting stability studies. Pharmaceutical manufacturers are expanding their global footprint, complicating the task of evaluating a drug substance or drug product as specific testing requirements can vary between markets. Further, the biopharmaceutical landscape is evolving with the emergence of novel, complex and diverse drug products.

An additional consideration when planning stability studies is whether to perform in-house or to outsource, considering the benefits and any possible issues relating to both approaches. Due to the need for controlled and monitored stability storage, implementation of multiple complex analytical methods, and specialized activities such as forced degradation studies (UV, oxidation, agitation, etc.), outsourcing may be the better option. Even if capabilities exist in-house, as development progresses, stability studies can generate hundreds of samples that need to be tested in a short period of time under varying conditions and configurations. This calls for extensive resources and a considerable amount of time and equipment usage, which may not be the best use of your laboratories' capacity.

Finding a single outsourced partner with the expertise and experience to develop an effective and streamlined stability testing program can be an attractive solution to reduce time and resources required to understand your product's stability. Not every provider can support with all the activities needed to execute a GMP stability study and whilst each may have different strengths, there is considerable value in working with a single partner that can support and coordinate all the activities to deliver an effective stability testing program that provides value to your organization in a highly competitive biologics development environment.

In addition, finding a partner with expertise in the modality or molecule type who can advise on and implement the testing packages needed to assess critical attributes for complex biological products as well as provide expert guidance to ensure adherence to the appropriate regulatory expectations can offer significant benefits.

The Value of a Consolidated Testing Organization

Working with a single consolidated outsourcing partner for stability studies offers a range of advantages:

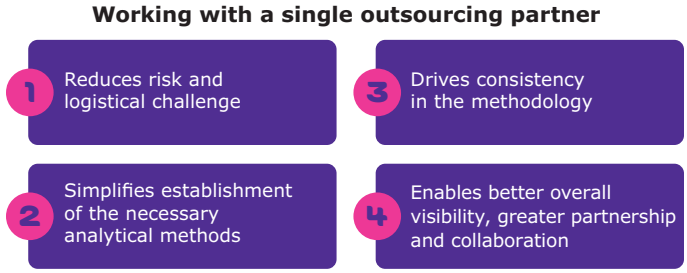

Figure 2: Working with a single outsourcing partner

- Reduces risk and logistical challenges presented by shipping samples to multiple organizations.
- It simplifies the establishment (transfer or development) of the necessary analytical methods at one provider and ensures consistency in the methodology, instrumentation, and data output provided. When using one laboratory, data is readily available to compare and analyze using the same parameters.
- Consolidates stability testing into one laboratory to drive consistency the entire study conducted under one quality system. This avoids challenges presented by differences in quality systems across multiple organizations. This can include variability in documentation, terminologies, and processes, which can complicate the task of assembling data packages for regulatory submissions and make interpretation by the relevant agency more difficult.
- Provides improved oversight since a single organization is managing the entire study, including storage, establishment of methods, timepoint sample testing, as well as protocol and report preparation, especially if the supplier offers a dedicated project manager. This enables better overall visibility, defined ownership, and ultimately responsibility, which drives successful execution of your study. This also fosters a greater partnership, collaboration, and common investment to advance the development of your therapeutic.

With the high costs and long timelines needed to bring a drug to market, improving efficiency and reducing risk wherever possible can accelerate your product development and de-risk complex studies such as stability. Consolidating stability testing with a single partner offers these benefits and more.

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