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Pharmaceutical Stability

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INTRODUCTION

Stability testing is the primary tool used to assess expiration dating and storage conditions for pharmaceutical produtcs. Many protocols have been used for stability testing, but most in the insudtry are now standardzing on the recommendations of the international conference on Harmonization (ICH). These guidelines were delevoped as a cooperative effort between regulatory agencies and industry officals from Europe, Japan, and the United States (Harman, 1999a).

Stability testing includes long-term studies, where the product is stored at room temperature and humidity conditions, as well as accelerated studies where the product is stored under conditions of high heat and humidity. Proper design, implementaion, monitoring and evalution of the studies are crucial obtaining useful and accurate stability data. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug production from early phase development through the lifecycle of the drug poduct. Stability data fo the drug substance are used to determine optimal storage and packaging conditions for bulk lost of the material. The stability studies for the drug product are designed to determine the expiration date (or shelf life). In order to assess stability, the appropriate physical, chemical, biological and microbiological testing must be performed. Usually this testing is a subset of the release testing.

PRECLINICAL STUDIES

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Precinical studies include standard staility studies to assess shelf life, but also utilize special studies to study the drug and its degradation characteristics. The drug substance charcterizattion and stability is usually determine as part of pre-formulation studies. Studies are chartacterzation degrade the solid drug substance and apporopriate solutions, allowing the determination of the degradation profile. The drug substance is usually challenged under a varitey of accelerated enviroment conditions to evaluate its intrinisic stability and degradation profile (Harman,1999b).

HPLC is the predominant tool used to analyze the drug substance and the impurities, particularly for small molecules. Frequently, the same HPLC method may be used for drug substance and drug product, although different sample preparation method would normally be required. Often the assay and impurity testing can be performed using a single HPLC method. However, the assay and purity determinations may also be separate methods. At least in the U.S., full validation of the analytical method is not required until the end of Phase 2 clinical trials, but the earliest stages, since verfication of stability hinges on a suitable method for seprating impurities from the active ingredient and at least quantifying the impurities realtive to the drug substance.

Stress studies at elevated temperature (e.g., 50 AC, 60AC and 70AC) for several weeks may be performed to assess thermal stability. Provided the degradation mechanism is the same at the different tempreatures used, kinetic or

statistical modles can be used to determine the rate of degradation at other tempretures (e.g., 25AC). The solid stability should also be performed in the presence and absence of water vapor to assess the dependence of stability on humidity.

Degration studies should also be performed in solution. The solvent for the solution testing will depend on the solubility of the drug substance and should include water, if the drug substance is water-soluble. Other solutions or solvent system may be evaluated depending on the anticipated formulation or the synthethic process. A series of buffered solutions in the pH range 2-9 are useful in assessing the impact of solution pH on the degration. Photostability should also be evaluted. A xenon light source can be used as a stress condtion. Alternatively, one can use an accelerates version of ethier Options 1 or 2 as discribed in the ICH guideline determination of photostability. Oxidation of the drug substance under accelerated conditoins (e.g., hydrogen peroxide), may also be performed to etablish oxidation product that could be formed and sensitivity to oxidative attack.

Early drug product stability studies are designed to help establish a suitable formulation for delivery of the drug substance. Compatibility studies of the drug substance with excipients should be performed to eliminate excipients that are not compatible with the drug substance.

CLINICAL STUDIES

Stability testing must be continued throughout clinical trials to support the safety, quality and efficacy of material relesed for clinical trials. Stability data must be submitted as part of the IND filing prior to initiating the Phase 1 clinical trial. Prior to the first Phase 1 stability study, the re-clinical studes should provide information on the appropriate long-term condition and the appropriate container/closure system. ICH Q1A provides the guidance for design of clinical stability studies. Selection of batches, the container closure system, specifications, testing frequncy and storage conditions are the imporant issues to consider when designing a stability study.

The container closure system must be evaluated for compatibility with the drug substance and drug product to ensure that the container does not contribute to degradation or contamination.

The testing frequency represents the minimum data required for filing. It may be advisable to pull and test a one-month sample for each storage condition to ensure that the study is proceeding as expected.

During Phase 1, it may be necessary to evaluate multiple formulations, dosage strengths and container closure systems. Using bracketing and/or matrixing can frequently reduce the resource allocation for these studies. These two design approaches are discussed in ICH Q1D. Bracketing uses the extremes to provide data for the entrie study may include testing of all strengths at the 25, 50 and 100 mg are to be evaluated, the study may include testing of all strengths at the initial and final time points with only the 10 and 100 mg strengths being teswted at the intermediate time points. Matrixing might be used to evaluate the same strenght in multiple container/closure system be selecting only certin container closure system for testing at each time-point. This selection is usually done in a random fashion.

At the end of Phase 1, the process for manufacture of the drug substance, and the drug product should be established (although

refinements will typically continue for much longer).

The time period in Table 1 represents the minimun data required for the NDA. The studies must continue until the long-term stability study is completed for the shelf life and retest period proposed in the NDA submission. Temperature cycling studies and in-use stability studies may be needed for certain types of formulations (particularly liqiud and semi-solid formulations). In early Phase 3 studies one should expect to be placing the batchs on stalibity (at least three drug substance and drug product lots) that wil be used for filing the NDA. These may be performed near the end of Phase 3 and adequate stability data for these batches may not be available at the time of filing. Shelf life and retest periods may be determine statistically with adequate quantitaive data.

The Period in Table 1 represents the minimum data required for the NDA. The studies must continue until the long term stability study is completed for the shelf life and retest period proposed in NDA submission.

Table 1 : ICH Q1A Summary of Stability Parameters

Study	Storage Condition	Minimum TIme Period	Comments
General Case: Long-term	25 ^{O}C + 2^{O}C/60 % RH + 5% RH or 30^{O}C + 2^{O}C/65% RH + 5% RH	12 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use
General Case: Intermediate	30 ^{O}C + 2^{O}C/65 % RH + 5% RH	6 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use
General Case: Accelerated	40 ^{O}C + 2^{O}C/60 % RH + 5% RH	6 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use
Refrigeration: Long-term	5 ^{O}C + 3^{O}C	12 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use
Refrigeration: Accelerated	25 ^{O}C + 2^{O}C/60 % RH + 5% RH	6 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use
Freezer: Long-term	--20 ^{O}C + 5^{O}C	12 months	Must cover retest or shelflife period at a minimum and includes storage, shipment and subsequest use

POST-APPROVAL (MARKETING PHASE)

At least one lot of drug substance and one lot of each packaging type for drug product produced each year should be placed on long-term stability. Addtional stability testing may be required to support process changes for drug substance and/or drug product. The filing requirements for changes are covered in multiple FDA guidance documents addressing drug product changes (SUPAC) and drug substance changes (BACPAC). Typically, this is an area that requires substanital regulatory understanding and experience to know how to proceed, and is beyond the scope of this article.

CONCUSION

Stability testing is interwoven through the entire fabric of the drug product life cycle. A detailed konwledge of the stability requirements and the impact on other areas (e.g., container closure, process shanges) is needed to properly design

and evaluate stability studies in order to ensure minimal delays and minimize cost in developing a new drug product.

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