Remington

Essentials of Pharmaceutics

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Chapter 4

Stability of Pharmaceutical Products

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INTRODUCTION

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications at a defined storage condition. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data include selected parameters that, taken together, form the stability profile.

The stability of a pharmaceutical product is investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salts stability/compatibility with various solvents, buffered solutions and excipients considered for formulation development. Suitable analytical methods must be employed in order to ensure the likelihood that this assessment will be successful. Optimization of a stable formulation of a pharmaceutical product is built (using statistical design) upon the information obtained from the preformulation stage and continues during the formulation development stages.

Typically, the first formulation development stage may be for preclinical studies or as late as the preparation of a "first in human" formulation which is often a non-elegant formulation optimized for short-term dose-ranging clinical studies. The second major formulation development stage occurs to support Phase II clinical studies (proof of concept phase). The pharmaceutical product developed at this stage is usually the prototype for the commercial product. Therefore, the pharmaceutical product will be formulated based in part on the stability information obtained from the previous formulations and must meet stability requirements for longer-term clinical studies. In the final formulation development state for Phase III clinical studies, the formulation must be truly representative of what the commercial pharmaceutical product will be in order to avoid delays in approval. In addition to building on the clinical requirements of the drug, the commercial pharmaceutical product must also incorporate the commercial or the final market image of the product, which includes the container closure system. The stability of this product must be demonstrated to the appropriate regulatory agencies in order to assign an expiration period and date for the product. This expiration period allows for the assignment of an expiration date based on the manufacture date of each lot of drug product.

Once a pharmaceutical product has gained regulatory approval and is marketed, the pharmacist must understand the proper storage and handling of the drug. In some cases, a pharmacist may need to prepare stable compounded preparations from this product.

Most drug products are not shipped directly from the manufacturer to a pharmacy. Typically, a drug product is shipped from a manufacturer to a distribution center. From the distribution center the drug product is then shipped to a wholesaler. From the wholesaler, the drug product may be shipped to the distribution center for a pharmacy chain or directly to the pharmacy. Finally, the drug product is dispensed by the pharmacy to the patient. Dispensing of the drug product may be at a hospital, a clinic, and a traditional "brick and mortar" pharmacy or from a mail-order pharmacy. Therefore, the stability typically must also assess the robustness of the drug product through its supply chain. It is not unusual for temperature excursions to occur during these transfers of control.

Inventory control, or holding, of each drug is important for a wholesaler or pharmacy. A drug must be within its expiration dating throughout its use by the patient. Solid oral dosages may be dispensed in the commercial packaging or in a pharmacy supplied container closure system. Most prescriptions are supplied to patients for up to 30 or 90 days by traditional and mail-order pharmacies, respectively. Inventory control of product by wholesalers and pharmacies must assess how much dating must remain on a product for it to be useful for its customer. This causes the actual holding of a product to be shorter than the expiration date. Under normal circumstances it is unusual for a pharmacy to accept any product with less than 6 month dating remaining on a product.

Much has been written about the development of a stable pharmaceutical product. Comprehensive treatments of all aspects of pharmaceutical product stability have been published by Connors *et al.*[1], Carstensen[2] and more recently by Allen.[3] This chapter will outline the appropriate steps from preformulation to drug approval to assure that the pharmaceutical product developed is stable. Requirements for compounded products will also be discussed.

The United States Pharmacopeia (USP) General Chapter <1191>[4] defines the stability of a pharmaceutical product as "extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of its manufacture." There are five types of stability that must be considered for each drug (Table 4-1).

The use of kinetic and predictive studies for establishing credible expiration dating for pharmaceutical products is now accepted worldwide. Scientifically designed studies using reliable, meaningful, and specific stability-indicating assays, appropriate statistical concepts, and a computer to analyze the resulting data are used to determine an accurate and realistic shelf life. In this way the maximum amount of valid information is obtained to establish a reliable, defendable expiration date for each formulation. The assigned expiration date is a direct application and interpretation of the knowledge gained from the stability study.

Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency

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