DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(8&9), 1413-1424 (1984)

STABILITY PROGRAMS FOR FORMULATION STUDIES

Gary R. Dukes

Quality Assurance Product Support
The Upjohn Company
Kalamazoo, Michigan 49001

ABSTRACT

The theme of this presentation is based on the premise that, despite the existence of differences in specific stability testing protocols between different types of products of the same manufacturer and between similar products of different manufacturers, it is possible to generalize somewhat and to identify elements common to any stability testing program. In terms of stability testing, a drug product may be viewed as passing through a series of distinct, identifiable stages in its development, which represents a progression of stability testing with product maturation. Within this progression, a range of testing protocols, methods and mathematical models may be utilized with each successive program designed to augment the data base of the product and thereby strengthen and expand the conclusions reached during each preceding phase. Differing types and amounts of information are sought at each stage which are important to the assignment of an expiration date, thus giving rise to widely differing concerns and objectives for each phase of the overall stability testing program.

0363-9045/84/1008-1413$3.50/0

INTRODUCTION

It is widely agreed by both pharmaceutical companies and government agencies that stability testing is a necessary and valid means to help assure that a product will maintain its integrity during its assigned shelf life. Also widely accepted is the reality of the existence of differences in specific stability testing protocols between different types of products of the same manufacturer and between similar products of different manufacturers. It would be futile to attempt to propose a simple, universal stability testing rule or formula which could be expected to reasonably assure the integrity of every product of every pharmaceutical manufacturer. In fact, within The Upjohn Company, widely differing concerns arise with respect to stability testing as a proposed new product matures into an established marketed entity.

While a number of factors may influence the determination of an expiry date for a given product, this discussion will be confined to testing designed to determine the chemical and physical properties critical to the stability of the product with the assumption that one or a combination of these is the limiting factor. Although much of the discussion may be applicable to the testing and dating of non-prescription products, it will be confined to prescription products which progress from investigational new drug (IND) status, through the new drug application (NDA) stage and on to marketing.

The theme of this chapter is based on the premise that despite the differences in specific stability testing protocols between products and manufacturers, there are elements which are common to any stability testing program. These elements may be categorized into four sets of activities: profile studies, assessment of stability, confirmation and expansion of stability data base and periodic reassessment of conclu-

sions. The relationship of these activities to an on-going stability program will be illustrated by a description of the program in use at The Upjohn Company.

The first set of stability-related activities in the development of a new active ingredient into a marketed product generally involves the profiling of its physical and chemical properties. This is followed by a period in which the stability of the bulk active ingredient and its associated formulations is assessed and an expiry date established. Subsequent to this assessment phase, stability studies are initiated and continued to confirm and expand the results of the preceding studies. Finally, the last phase is one in which the stability of the marketed product is periodically reassessed.

Thus, the development of a new active ingredient into a marketed product may be viewed as a progression of stability testing with product maturation. While the emphasis of the discussion to follow is on the stability program for formulation studies, it is important to place these activities in the context of an overall, integrated stability program for new product development. Within this progression from profile to assessment through confirmation and expansion and finally to periodic reassessment of product stability, a range of testing protocols, methods and mathematical models may be utilized, with each successive phase designed to augment the data base of the product and thereby strengthen and expand the conclusions reached during each preceding phase. Differing types and amounts of information are sought at each stage which are important to the assignment of an expiry date, thus giving rise to widely differing concerns and objectives for each phase of the overall stability testing program.

STABILITY PROGRAM BY PHASES

Four phases of stability-related developmental activity may be identified and related to the progress of a new, active ingredient from IND status through the NDA and on to marketing.

NEW ACTIVE INGREDIENT STAGE

This represents the time from discovery of possible therapeutic usefulness of a new drug substance through the time of filing of an IND. The objectives of this stage are the following: (1) to profile the chemical and physical properties of the active ingredient to determine factors promoting degradation, (2) to identify probable routes of degradation and any degradation products which result, and (3) to develop an assay which is specific for the active ingredient in the presence of process impurities and degradation products. The profile of properties should include such information as solubility in various solvents, crystal form(s), structure, spectral features and hygroscopicity. In order to identify probable routes of degradation, the active ingredient should be subjected to conditions of stress, such as heat, light and moisture. Degradation products which are formed during these studies should be identified and an assay specific for the active ingredient in the presence of process impurities and degradation products developed. At this point, long term stability studies of the active ingredient under expected production storage conditions (i.e., room temperature or refrigerated conditions) may begin. In many cases, the assay developed at this stage for the bulk drug is later adapted for the quantitation of the active ingredient in various experimental formulations in the product candidate stage. In addition, information gained from the study of the active ingredient constitutes the first portion of kinetic data which may ultimately be important in assessing a product's shelf life.

PRODUCT CANDIDATE STAGE

This covers roughly the period from IND filing through NDA submission and approval. The emphasis in this phase shifts from profiling the physical and chemical properties of the bulk active ingredient to the assessment of the stability of both the bulk drug and its associated dosage forms as they are developed. Early in this stage, additional studies specific to the type of formulation chosen are conducted on the bulk drug to complete the profile of its physical and chemical properties. The effects of pH upon solution stability[1], for example, would be critical if the active ingredient were to be formulated as an aqueous solution or as a reconstitutable solution. If the product is to be formulated as a suspension, studies to determine changes in particle size with changes in temperature or over time would be very useful. A knowledge of the various crystal forms in which the active ingredient can exist and the solubilities of each could prove very important to the dissolution properties of tablets or the bioavailability of oral suspensions[2].

The objectives of this stage of product development are threefold. The first is to assess the stability characteristics of the selected formulation for the purposes of identifying stability-limiting factors and defining optimum storage conditions. The degradation pathways in the selected formulation are confirmed in this phase and the accuracy and specificity of the potency assay are validated. The third objective involves determination of the shelf life for the selected formulation in the container/closure system in which it is to be marketed.

In order to select the optimum formulation, a three-phase screening program is utilized. The first phase involves testing several trial

formulations under accelerated conditions and evaluating each on the basis of physical factors. For example, a compressed tablet may be subjected to strong light to determine if fading or discoloration occurs[1] and to conditions of heat and elevated humidity to test for any tendency to harden or soften. A suspension may be subjected to freezing to determine the effect on its suspendability while a solution may be subjected to refrigerated conditions to ensure that precipitates are not formed. Ointments and creams may be subjected to high temperatures to determine the relative tendency toward separation.

EXPERIMENTAL FORMULATION SCREENING

The second phase involves screening the experimental formulations for chemical stability. Utilizing the assay for the bulk drug from the previous stage, an assay is developed for the most promising formulations. Specificity may be determined by spiking the assay preparation with like compounds or authentic samples of bulk drug degradation products.

Extensive use is made of high temperature and high humidity conditions[3]. For example, the experimental formulations may be stored at 40°, 47°, 56° and 70°C and assayed for potency at several intervals. If there does not appear to be a change in the mechanism of the degradation reaction, Arrhenius plots may be utilized to calculate energies of activation and the shelf life of the proposed formulations at other temperatures may be estimated. Regression analyses are also performed to provide a crude estimate of the shelf life of each formulation. The shelf lives estimated from the use of the Arrhenius plots and the regression analyses are used to compare the formulations to each other in order to determine the one which is most stable. The data for the

selected formulation are also useful in providing the first indications of a suitable storage condition for the finished product.

Those formulations which have survived both the physical and chemical screens and for which bioavailability may be a concern are then subjected to further screening which involves both dissolution testing and animal studies. Assay development work is performed to ensure that an adequate method for detection of the active ingredient and decomposition products are available. As in the chemical screen, extensive use is made of high temperature and humidity conditions to determine the relative sensitivity of the bioavailability of the formulations to stress.

On the completion of these portions of the screening phase, the optimum formulation is selected. The assay for the active ingredient is then carefully validated and kinetic studies are conducted to verify its degradation pathway, identifying any previously undetected degradation products.

CONTAINER/CLOSURE SYSTEM SELECTION

The last component of the screening phase involves studying the selected formulation in several different container/closure systems. Conditions of elevated temperature and humidity are used to determine the stability characteristics of the formulation in the various container/closure systems. Some types of containers may already have been excluded due to data obtained in the previous portions of the screening phase. For example, a clear flint glass bottle would not be considered for a tablet which is known to discolor on exposure to light. Test and assay data are obtained and regression analyses are used where applicable to obtain crude estimates of shelf life for comparison purposes.

In many cases, physical factors will rule out certain container/closure systems. For example, the use of barium-containing glass for a solution of a sulfate salt of an active ingredient would be likely to suffer from problems of partculate formation problems. Moisture permeation may cause tablet softening in vinyl blisters[4] and incompatibility between a solution or suspension and a rubber stopper may result in either discoloration of the solution or the stopper or the formation of particulates. Any packages which are found to adversely effect product stability are eliminated.

LONG TERM STABILITY STUDIES

Once the formulation and container/closure systems are chosen, the stability studies to be conducted over a longer term (one to two years or more) may be defined. Their purpose is to define optimum storage conditions, identify stability limiting factors for these storage conditions and determine a shelf life for the product in each of the container/closure systems in which it is to be marketed. These studies provide the data submitted in the NDA (or Antibiotic Application) which are directly supportive of the proposed expiry dating.

In general, at least three to five lots of the proposed formulation are placed on test in the selected container/closure system(s) to be marketed and are studied under conditions consistent with the proposed product labeling. These lots are usually produced in production-scale equipment. When stored at proposed label storage conditions, they are tested and assayed quarterly during the first year, semi-annually in the second year and annually thereafter. The higher density of data gathered in the first two years gives timely assurance that the conclusions about product stability from earlier studies are confirmed and expanded.

By the time an NDA is filed, the proposed expiry dating of the product is backed by the stability data gathered up to this point which includes the following:

1. bulk drug studies
2. pre-formulation studies
3. studies of the various container/closure systems
4. studies of the selected formulation in the selected container/closure system(s) stored under the proposed label storage conditions.

In the optimum case, by the time of expected NDA approval, the assigned expiry dating is supported by a full data base as well as a good deal of stability experience and the length of the assigned shelf life is less than or equal to the number of months of stability data at label storage conditions in which the various product parameters remained within the proposed product specifications. In such a case, there is no need to rely on any kinetic models or assumptions and the validity of one data manipulation method relative to another is really unimportant. Particurly important is the confidence that the product will meet specifications for parameters which are not easily predictable from testing conducted under accelerated conditions, such as dissolution behavior.

NEW PRODUCT STAGE

At the time of NDA approval and initial marketing, development enters the New Product Stage during which concern shifts from assessment of stability characteristics and assignment of an expiry data to one of confirmation and expansion of the stability data base. In this stage, which covers the first several lots of full-scale production for market-

ing and usually lasts for one year after market introduction, the studies initiated during the Product Candidate Stage are continued and, in general, at least three production lots are placed on stability. The frequency of testing is based on the assigned product shelf life. If the shelf life is less than 24 months, tests and assays are run every six months for the first two years and annually thereafter. If the shelf life is 24 months or greater, tests and assays are run annually. Replicate assays are run at early intervals to allow early warning of any product problems.

Regression analyses are performed periodically on test or assay data and the time it would take for important properties to reach product specification limits is estimated from the regression lines. These estimated shelf lives are used to confirm the shelf life of the product which was determined during the Product Candidate State or to act as an early warning mechanism that the shelf life may have changed. When warranted, any ultimate revisions of the shelf life for the product are supported by a full data base.

ESTABLISHED PRODUCT STAGE

During the Established Product Stage, which includes the time period covered by all other manufacture of the product, concern again shifts. At this point, a comprehensive data base is in place and the objective becomes one of periodically reassessing the stability of each product.

Because much stability data has been generated on the product during the preceding stages, generally less data per product is required in any given time span during this continuation of the stability testing program. For example, for Product X with its 18-month shelf life, two

lots per year per dosage strength would be added in the Established Product Stage. Product Y with its 48-month dating would have one lot per dosage strength added annually. The assay intervals and number of replicates per interval for Product X would be identical to that in the New Product Stage, while Product Y, a more stable entity, would be tested on a reduced scale. The lots would be rotated among the marketed packages. Members of product families having different dosage forms are considered to be separate entities and each member is treated as a separate, distinct product. As in previous stages, assay data are collected and regression analyses are performed frequently as a diagnostic tool to warn of changes in shelf life.

It should be borne in mind that the above discussion reflects the stability testing procedures as they have evolved over the years at The Upjohn Company; they will undoubtedly be refined and improved in years to come. However, it is hoped that the above discussion has succeeded in stimulating some thoughts regarding the elements common to all stability testing programs. In particular, while the finer details of stability testing programs may differ, the concept of a progression of stability testing with product maturation - a system guaranteeing a certain continuity of data augmentation - should be applicable to any stability program.

REFERENCES

1. J.J.Winheuser and T.Higuchi, J. Pharm. Sci., 51, 354 (1962).
2. A.J.Aguair, J.Krc, Jr., A.W.Kinkel and J.Samyn. J. Pharm. Sci., 56, 847 (1967).
3. J.T.Carstensen: "Solid Pharmaceutics: Mechanical Properties and Rate Phenomena", Academic Press, 1981, pg. 243-244.

4. M.Veillard, D.Duchene, R.Bentejac and J.T.Carstensen, Drug. Dev. and Ind. Pharm., 5, (3), 227 (1979).

5. L.Lachman, S.Weinstein, G.Hopkins, S.Slack, P.Eisman and J.Cooper, J. Pharm. Sci., 51, 224 (1962).