DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 5(4), 349-363 (1979)

STABILITY TESTING FOR EXPIRATION DATING*

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ABSTRACT

The use of stability testing and expiration dating as a tool for assuring product integrity is generally accepted by pharmaceutical companies and governmental agencies alike. Equally accepted is the notion that it would be impossible for anyone to forward one simple stability testing formula or rule for reasonably assuring the integrity of every product of every manufacturer. In fact, within The Upjohn Company, widely differing concerns arise with respect to stability testing as a proposed new product matures into established product status. The purpose of this presentation is to discuss some of the objectives and operational

* Presented at the "Purdue Management Conference for the Pharmaceutical Industry", Purdue University 9/13-15/1978, West Lafayette, Indiana.

procedures used at Upjohn with respect to the stability testing of a product at various stages in its existence.

What I would like to present to you today are some general thoughts concerning stability testing for expiration dating. The theme of my presentation is based on the premise, that for stability testing purposes, a prescription drug substance progresses through a series of distinct, identifiable stages in its existence. Within each stage, differing pieces of information important ultimately to assigning an expiration date are sought; and this progression gives rise to widely differing concerns and objectives for each stage.

Before continuing on, perhaps it would be worthwhile to lay some ground rules. First, it is well recognized that many factors may influence the determination of an expiration date for any given product. For instance, if the chemical and physical stability of the formulation are not the limiting factors, then business decisions regarding packaging wear-and-tear or the seasonal nature of the product may have the greatest influence on the shelf-life of the product. The following discussion about stability testing will be confined to testing designed to determine the chemical and physical stability with the assumption that either is the limiting factor. Second, while many of the thoughts may apply to the testing and dating of over-the-counter, non-prescription, products, the presentation will be confined to prescription products which progress from investigational new drug status, through the NDA, to marketing.

As you will see, this presentation is not meant to be designed to tell you exactly how many lots of each of your products to study or at what temperatures they must be stored. It is not meant to tell you how to assay your samples or how many times they should be assayed per year. And, most surely, it is not designed to tell you what model to use to analyze your data or how to use the results to assign a valid shelf-life to a product. Instead, I hope to suggest today that a range of testing protocols, methods, and mathematical models may be of use and that differing sets of these parameters may be more important depending on the product's stage of development. The stability system I will discuss has evolved over the years and is the essence of our own program at Upjohn. I will be mentioning specific particulars and details.

But, in the end, each manufacturer must choose the factors important to assuring the integrity of his own products. Which factors are chosen will, over time, become strong contributors to the success of that product.

Given the overall goal of having a firmly established product on the market whose integrity over its dating period is assured by a sizable data base, we have found that, with respect to stability testing, different activities are required for the following 4 progressive stages of product development:

1. The first stage is what we call the New Active Ingredient Stage:

This stage represents a time when a new drug substance, a new chemical entity, is being considered for the filing of an IND.

2. The second stage is the Product Candidate Stage:

This covers roughly the pre-NDA period when the drug dosage form studies are being carried out.

3. Next is the New Product Stage:

This stage covers the first several manufactured lots for distribution, usually within two years of the first marketing.

4. The product then progresses to the Experienced Product Stage:

This stage represents all the time of manufacture after approximately the first two years of routine production.

At Upjohn, we have ongoing programs to cover each of these four segments. Each successive program is designed to augment the data base of the product and thereby supply assurance that the conclusions reached at each preceding stage are strengthened and expanded.

Lets now look at the objectives and activities beginning with the New Active Ingredient Stage.

The foundation of any stability system is the integrity of the tests and assays used to monitor the critical factors. In the case of potency, it goes without saying that the assay must be specific for the active ingredient in the presence of its degradation pro-

ducts. It follows that the possible degradation paths of a new drug substance must be investigated and defined. The stability objectives of the program associated with new active ingredients are simply stated as:

A. identify probable degradation routes of the new active ingredient, and

B. develop an assay which is specific for the active ingredient.

In the process of accomplishing these objectives, new active ingredients may be forced to degrade by various methods, such as subjection to high heat, moisture, and light levels. Any resulting degradation products are identified and a specific assay is designed. Often, the assay developed at this stage is later adapted to test the active ingredient potency in various experimental formulations in the product candidate program. The degradation studies in the New Active Ingredient stage often supply the first bits of kinetic information important in assessing future product shelf-lives.

In the product candidate program the stability objectives are to:

A. determine the stability limiting factors and optimum storage conditions for the selected formulation,

B. confirm degradation pathways in the formulation and validate the accuracy and specificity of the potency assay, and

C. determine a dating period or shelf-life for the selected formulation in the container/closure system to be marketed.

In the early stages of the proposed product program, preformulation studies are carried out to further determine the degradation characteristics of the active ingredient. For instance, solution stability as a function of pH would be a critical study if the final product is expected to be a liquid.

When the most promising formulation or formulations are developed, their stability characteristics must be assessed. In the course of these studies samples may be routinely stored at 4°, 25°, and 37°C. In addition, extensive use is made of high temperature and high humidity data. For instance, a proposed formulation might be stored at 40°, 47°, 56°, and 70°C; and then assayed for potency at various intervals. If the data are determined to follow simple kinetic models, an energy of activation can be used to determine the stability of the formulation under a different range of temperatures. Regression analyses are performed to estimate a crude shelf-life for the product, or in some cases, to compare the stability of one formulation to another. Concurrently, tests are performed to identify aging and heat sensitive properties. A small stability data base is established which will be instrumental in determining the probable storage conditions and will serve as the basis for further stability testing.

Also, during the product candidate stage, the stability of the selected formulation is studied in several of the proposed

market container/closure systems. Again, accelerated temperatures and humidities are used to determine the effects various market packages have on product stability.

Test and assay data are collected and regression analyses are used to estimate a crude shelf-life for comparison purposes. At this point in time, if market packages are identified which do not provide adequate protection for product stability they are eliminated from consideration.

Generally 3 to 5 lots of the proposed product are studied in the selected market container/closure system or systems under conditions consistant with the proposed product labeling. These lots are produced using at least 3 different batches of the active ingredient in order to assure that possible lot-to-lot differences in the active ingredient result in no discernable effect on product stability. In addition, these product lots are to be manufactured in production scale equipment. The lots are assayed and tested quarterly for the first year, semi-annually for the second year, and annually during the remaining years. The higher density of data gathered in the first two years gives timely assurance that the conclusions about the product stability from earlier studies are validated and expanded.

At the time an NDA is filed, the proposed dating of the product is backed by the stability data gathered up to this point in time which, in summary, includes:

1. bulk drug studies
2. various pre-formulations studies

3. studies of the various possible market packages, and
4. studies of the selected formulation in the selected container/closure system stored under the selected storage conditions.

In the optimum case, at least by the time of the expected NDA approval, the dating assigned is backed by a full data base and backed by a good deal of stability experience. That is to say, the length of the assigned shelf-life is less than or equal to the number of months of available stability data in which the various product parameters remained well above 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. The only uncertainties remaining are the reproducibility of full scale production operations and the reproducibility of the tests and assays performed in a routine setting. Monitoring these uncertainties and their effects on the dating period is the function of the New Product Program instituted with newly marketed products.

The stability objectives of the New Product Program are simply to:

A. evaluate and expand the conclusions reached in previous studies concerning the stability of the formulations as production becomes full scale, and
B. provide data for adjustment of the shelf-life if warranted.

In this program, usually three production lots of each product are selected. More production lots are selected if there are several marketed container/closure systems. The frequency of the assays performed for each product is based on the shelf-life of the product. Assays are scheduled more frequently for a product with a short shelf-life than for one with a long shelf-life.

For instance, if product X were assigned a 24 month shelf-life it would be scheduled for assay every three months in the first two years. If product Y had a 60 month dating, it would be assayed every six months in the first two years, and then yearly thereafter unless the analysis of the data indicated a shorter shelf-life would be appropriate. In this manner, the total amount of data collected for each product over its shelf-life is roughly equivalent.

With respect to data analyses in this program, regression analyses are performed periodically on test or assay data showing trends. The time it would take for important properties to reach product specifications is estimated from the regression line and used to validate the shelf-life of the product 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 again supported by a full data base.

The continuous validation of the stability of firmly established products is the sole stability objective of the Experienced Products Program. In this program, production batches of products are

monitored in a constant fashion to provide the final assurance of a product's integrity over its shelf-life.

Because much stability data has been generated on a given product from the previous programs, generally less data per product is required in any given time span. In keeping with the notion that the amount of data needed per product per year depends on the shelf-life of the product, more lots per year are added and a higher frequency of assays are scheduled for the more unstable products. As an example, consider product X again with its 24 month shelf-life. In the Experienced Products Program, one lot per year would be added and it would be assayed twice per year over its shelf-life. Product Y with its 60 months would have a lot added every other year and be assayed once per year. Products with shelf-lives in between are prorated accordingly.

Members of product families having different dosage forms or different concentrations of active ingredients in the same dosage form are considered to be separate entities and each member is treated as a separate, distinct product.

Again, assay data are collected and regression analyses are performed periodically on the data as a diagnostic tool to warn of shelf-life changes.

What has been described thus far, is a fairly straight-forward sequence of programs for assessing product stability. The quantity of data and experience with the product steadily increases as the product progresses. In the early stages, before product

marketing, Arrhenius and regression analyses are used primarily for evaluation and screening in pre-formulation studies and in the selection of container/closure systems. In the latter, marketing stages such analyses are used for early warning of stability changes. In many instances the assignment or adjustment of a shelf-life can be made with much experience and much data at storage conditions consistent with label storage statements.

There are, perhaps, nearly as many instances, in which the number of months of directly supportive data is significantly less than the number of months of the proposed dating, which experience would indicate as entirely reasonable.

I am refering, of course, to product revisions. If the programs previously discussed are conscientiously implemented; treating revised products as entirely new products requiring a full, directly-supportive data base is neither advisable nor necessary.

Changes in products can occur in several fashions for a multitude of reasons. In general we categorize them as, Formulation Changes, Processing Changes, and Packaging Changes.

A. Formulation Changes:

Formulation changes include the addition or deletion of excipients, the adjustment of active ingredients, and the like. Reformulations can occur due to changing governmental regulations, the availability of raw materials,

or the identification of physical stability problems.

B. Processing Changes:

Processing changes include changes in the method of manufacture of the formulation or changes in manufacture of the bulk drug which could affect physical stability.

C. Packaging Changes:

Packaging changes include a change in the container/closure in direct contact with the product such as switching from a glass container to a plastic container. These changes are usually due to the availability of materials or market demand.

When a change is made in one of our products a decision is made regarding the possible impact of that change on the stability of the product. For changes considered insignificant, no special studies are performed. Production lots of the product are added to the Experienced Product Program and tested and assayed according to the appropriate schedules and procedures. The data are monitored for early changes in the shelf-life by regression analyses. Many formulation changes involving the deletion of minor excipients are treated in this fashion.

There is no set rule which allows us to determine when a change will have a significant impact on product stability. A sound technically-based understanding of the product's decomposi-

tion pathways and physical stability developed in the early stages of the new product program is the key to making reasonable decisions. When the decision is made that a particular change may have an impact on the stability of a product; the product is entered into a revised product program. The first matter deserving attention is validation of the stability indicating assay. New excipients or different excipient ratios can interfere with the assay previously developed. Demonstrating accuracy, precision and the specificity of the assay for the revised product is essential.

With respect to testing revised products, two segments may be implemented. In the first segment of the program one production lot of the "old" product and one research lot of the revised product are stored under accelerated conditions and assayed regularly over a 6 to 9 month period. This allows us to obtain a rapid comparison of stability performance. In the event these accelerated studies indicate that the product is likely to be significantly less stable after revision, more changes are obviously in order.

In the second segment of the program, 3 production lots of the revised products are stored at label conditions. Samples are assayed every three months for the first year, every six months in the second year, and then yearly for any appropriate additional years. If early data analysis indicates a faster degradation rate than anticipated, more data are taken in the second year.

The shelf-life assigned to a revised product may be equal to or less than the shelf-life established for the "old" product.

In the optimum case, enough stability data, gathered from samples stored at label conditions, are available so a reliable regression analysis may be performed to yield a shelf-life. In this determination manufacturing and assay variations must, of course, be appropriately accounted for.

In the instance when reliance on a regression analysis is questionable, the determination of the shelf-life reflects the amount of available, indirectly-supportive stability data and the back log of general product experience. In most such cases, the shelf-life assigned is much shorter than that established for the "old" product.

In all instances, samples remain in the revised product program and are monitored so a full data base may be achieved to further establish the assigned shelf-life. When a full data base is obtained, the revised product progresses to the experienced product stage. As discussed before, it is then continuously monitored for changes.

In closing, permit me to reiterate that my discussion reflects the stability testing procedures which have evolved over the years at Upjohn. They will undoubtedly be refined and improved in the years to come. While the concept of a progression of stability testing with product maturation - a certain continuity of data augmentation - may be applicable to the programs of other

companies, the finer details must be a function of product mix and product experience.

Ultimately, the validity of any chosen combination of testing methods, protocols, and dating procedures is determined by the stability performance of the product in the market place.