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GMP ASPECTS OF STABILITY PROGRAMS

Joel S. Davis

Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

18.1 Introduction

Prior to the current regulations in the United States governing good manufacturing practices (GMPs) for finished drug products (1), expiration dates were only required for drug products liable to deterioration or for drug products listed in the United States Pharmacopeia (USP). While GMP regulations required stability of a drug product to be determined, it was not until the publishing of the current regulations that specific mention was made as to what should be included in a stability program. Regulations such as these are designed to be applied like product specifications. They are a guide to acceptable quality and provide what is considered minimal to achieve this quality. An analogy would be a USP monograph specification for strength of 90 to 110 %. In order to assure this strength, the manufacturer will usually design a process to achieve a product with even closer tolerances. In addition, requirements determined by a government reviewer for a particular drug entity of dosage form may be more rigid than those found either in regulations or in agency guidelines, since there may be unique characteristics of a particular drug entity or dosage form that may require special testing or monitoring to provide assurance of a product's integrity.

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The regulations require not only that drug stability be determined but that the firm have a written stability program and the progress be followed. While the regulations do not provide us with definitions of the elements of a stability program, several criteria are presented which should be included in the program. The first criterion of a stability program is that it specify the sample size and test intervals for each attribute to be examined. Recommended test intervals for new products have usually stressed a greater frequency of testing during the first year or two, e.g., testing initially, then at 3,6,9,12,18,24, and 36 months. Such testing allows the analyst to determine a trend of degradation early in the shelf life of the drug. On the other hand, if initial stability is predictable, possibly from accelerated studies or a previous product history, the program may be more appropriately designed if it provides for more frequent sampling closer to the anticipated expiration date. The size of the sample must provide assurance that it is representative of the batch. Likewise, the number of batches chosen for sampling must be adequate so that analysis demonstrates a consistently manufactured product from batch to batch. Performing stability studies on at least three batches of product seems to be the minimum that is usually acceptable. Whenever a change in the formulation, packaging, manufacturing process, or manufacturing facilities occurs, at least the first three consecutive production batches after such change should be placed back into the product stability program to definitively establish that such change has not adversely altered the established expiration period of the product.

18.2 Significant changes

Often the question is asked, "What kind of change is significant enough to warrant additional stability studies?" The answer is that any change or substitution in either the product formulation, manufacturing procedure, or in packaging may be critical to the overall product integrity. Should a manufacturer consider a change to be insignificant, data should be available to substantiate this belief. While, at one time, changes of excipients were considered to be minor, it has been demonstrated that changing merely the

quantity of excipients such as starch, sodium lauryl sulfate, or ethyl cellulose may, in fact, critically alter a product's stability. Reprocessing a finished dosage form, changing a procedure, e.g., lyphilization to spray drying, or extra milling of ingredients, may subject the drug to additional heat and/or moisture which could alter previous conclusions as to a product's stability.

The next requirement of the stability program is that the storage conditions of samples retained for stability studies be stated. Because of the possible interaction of a stopper or cap liner with an ingredient, it is good practice to store solutions in a manner that provides contact of the contents with the closure system. For instance, liquid products should be stored either on their side or in an inverted position. Storage conditions during stability studies should also reflect the actual extremes of temperature, humidity, and light that the product may be subjected to during anticipated storage in the marketplace, unless the product label bears specific instructions as to storage, i.e., refrigerate, or protect from light. Obviously, if a product is photosensitive, it should not be stored in the dark, but subjected to appropriate light intensities. (2) Stability studies should allow for special storage conditions necessary for certain dosage forms. For example, emulsions have unique properties that can be stressed through cyclic temperature studies. (3)

18.3 Test Methods

The regulations require that the test methods utilized for determining product stability be first reliable, then meaningful and specific. I must emphasize method reliability is of prime importance. A reliable method is one that survives the classic analytical challenges of precision, accuracy, reproducibility, and ruggedness. Employment of sophisticated analytical equipment and techniques in itself is not a criterion for a reliable method. In fact, often the use of such equipment presents special analytical problems that must be resolved. While the U.S.P. refers to a system suitability test in certain monographs, (4) the reader would do well to consider such testing

as a fundamental analytical technique for analysis of products other than USP articles also.

A meaningful test refers to a procedure that is appropriately designed to obtain necessary information. Should a product be subject to degradation by light, any test to examine for potential degradates would be meaningless if the product had been stored in an unlit area. Another example of a test that would not be meaningful would be a test performed at high temperature and low humidity for a product that would be likely to degrade by hydrolysis. The conditions of such a test might provide a less challenging environment than would storage at ambient conditions.

For the test to be specific, it must have the potential to differentiate the drug under assay from products of chemical degradation and from other ingredients in the formulation which might interfere. Often, chromatographic techniques are utilized ro separate closely related compounds. One cannot make the assumption that, when only one spot is detected or one peak resolved, the method is specific unless it can be adequately demonstrated that degraded compounds could have been detected. That is, the method must be sensitive enough to identify small amounts of a degradent and adequately resolve them from the parent drug. Reliable, meaningful, and specific testing need not be confined to a single assay. Often this may be impractical. As long as multiple tests are available which accomplish the same objectives, they may be utilized.

18.4 Packaging

The stability program is also required to provide for testing of the drug product in the same container and closure system as that in which the drug product is marketed. At times this has been interpreted rather liberally, but extrapolation should be based upon scientific rationale. For instance, if a manufacturer had developed stability data for a tablet that was packaged in a polystyrene container and a repacker plans to market the tablets in a glass container, the FDA has commonly agreed to such a change because the literature indicates that glass is probably the most impervious barrier

to moisture. In such cases, FDA has condoned a repacker labeling the product with the same expiration date as on the original product. However, a similar change for a liquid product might not be suitable because the alkaline nature of glass is known to affect the pH of a solution to the extent that product integrity has been jeopardized by such a change. Generally, if data is available that indicates a particular container or closure may be better than that employed, it may be used with the previously established expiration dating period as long as the newly packaged product is reintroduced into the stability program as previously described. A simple mechanism of assessing the suitability of two container systems is to test one against the other for moisture permeation, particularly at temperatures higher than room temperature.

If the same inner seal is employed or the same cap liner is used, changes of the cap design may not warrant the performance of additional studies. The torque applied to the cap may be of importance, particularly if an innerseal is not employed.

Testing the product packaged in the smallest marketed container is usually the most critical size to test since the ration of internal area of the container to the contents is more critical to product integrity the smaller the container. Very often the amount of air in a smaller container is greater in proportion to the ingredients also. It is considered GMP to test not only the smallest container but also the largest. If there are large differences in extremes of product sizes, intermediate sizes should not be overlooked when testing.

The packaging or repackaging of drugs into unit dose containers requires special knowledge of these types of containers and techniques for sealing the package. The USP provides performance standards for several classes of unit dose container packages. (5) In an effort to encourage hospitals to dispense drugs in such containers, FDA decided that, should drugs be repacked in unit dose containers that meet or exceed the quality of a type B container, as defined in the USP, an expiration date of not more than six months from packaging could be placed on the container label, and FDA would not require

that stability data be obtained to verify that date. This is also dependent on the condition that the six month period be not more than one-fourth of the remaining expiration date on the stock bottle at the time of repacking. Any expiration date greater than six months must be substantiated by standard procedures as described above.

It is not advisable to extrapolate from one material to another when packing into unit dose containers without considering the sealing technique of the materials utilized. In this type of system it is not only the foils and plastics that provide protection to the drug, but the manner in which the materials are joined that prevents the adventitious entrance of air or moisture.

18.5 Reconstituted Products

Regarding products intended for reconstitution, the regulations specify that the stability program shall include testing of the drug at the time of dispensing (following the directions on the label) and after the drug is reconstituted. This is necessary to support the requirement that there be essentially two expiration dates on this type of product: one for the reconstituted product, and the other for the product after reconstitution.

18.6 Accelerated Studies

The GMP regulations of 1978 allow for the first time the use of accelerated studies to support an expiration date. Combined with basic stability information on the components, dosage form, and container closure system, accelerated testing may provide the basis for an expiration date that is beyond a date supported by actual shelf life studies. When an expiration date is tentatively established in this manner, stability studies must be conducted and the product tested at appropriate intervals until the tentative date is either verified or the valid expiration date determined.

There is neither a standard which specifies what constitutes an accelerated stability program nor a universal test applicable to all products. Several years ago I suggested conditions for a test which might be applied to solid dosage forms and which was not intended to be ideal for all products, but could

be applied in the majority of circumstances. The test is to subject the product (dosage form in the container-closure system used for marketing) to 40°C and a relative humidity greater than 75% for three months. A product still complying with its particular specifications after this test would be acceptable for a labeled expiration dating period of two years. If a product is known to have stability problems or is a new drug where little may be known of its relative stability, an accelerated test such as above may not be suitable. Other more rigorous accelerated testing employing multiple temperatures or the cycling of temperatures may be more appropriate for some products. The proposed test of 40°C and 75% relative humidity for three months is really designed as a stress test for the dosage and container-closure, not as a true kinetic test. Even though the drug substance may not degrade by hydrolysis, the high moisture of the test is important because it severely stresses the product. For example, some tablets after absorbing only a few percent of water have been shown to fail dissolution specifications. The test to be properly monitored should have assays run initially and at least monthly. The above conditions could also be used as a stress test for liquid products; however, this would no longer require the use of high humidity as a test parameter.

The use of the Arrhenius equation to predict the kinetics of degradation has been applied extensively to chemicals in solution. The researcher will usually choose a chemical for such a study that degrades quite easily. After all, if the purpose of the research is to monitor degradation kinetics, there would be little value, if any, in selecting a chemical that demonstrates only minimal degradation. The single chemical in solution comprises the typical kinetic study. However, once that chemical is incorporated with several other ingredients, some of which may be equally or more reactive, and then compressed into a tablet or filled into a gelatin capsule, a new and unique set of circumstances exists. This new cosmos could alter the degradation behavior of that chemical which was previously monitored only by itself.

There is little in the literature that reports subjecting dosage forms to either kinetic or accelerated testing. A paper by Lloyd Kennon (6) considered the need for testing the finished product. By limiting the heat

of activation to 20 Kcal/mole, he rearranged the Arrhenius equation in such a way to allow variables of time and temperature and developed an easy to follow scheme of predicting expiration dates. I believe that Kennon's restriction of 20 Kcal/mole might be unnecessarily conservative since most drug substances probably have a heat of activation far greater. For instance, the literature reports that ascorbic acid and epinephrine have heats of activation as high as 24 and 23 Kcal/mole, respectively. (7) (8) Both of these drugs are generally considered to be easily degradable compared to most. While the average heat of activation reported in his article was 19.8 Kcal/mole, Kennon notes that these heats of activation necessarily fall in a range which made study of the reactions convenient. He also, quite reasonably, points out that many drug compounds' degradation reactions must have heats of activation higher than those he references.

Yang and Roy (9) and Fung (10) independently analyzed my proposed stress test of 40°C-75%-3 months concluded that for products with a heat activation of at least 25.8 Kcal/mole the test is valid. These researchers, of course, made certain assumptions. One was that, in order to make the equation work, degradation was held at a constant of 10% loss. Therefore, if an accelerated test should show less than 10% degradation over the three month interval, one could utilize the parameters for compounds with heats of activation proportionately less than 25.8 Kcal/mole. As an example, Figure 1 is based upon the paper by Yang and Roy and shows that should degradation be as low as 10% after three months at 40°C and 75% relative humidity, the corresponding heat of activation would be 25.8 Kcal/mole. Figure 2, on the other hand, shows the same plot but allows for only 5% degradation. Under these conditions, the threshold energy could be any value in excess of 17 Kcal/mole.

Witthaus (11) also reviewed my proposal but used a somewhat different approach. He points out that if the activation energy is known beforehand, or it can be estimated by analogy, a prediction of expiration date is possible even after testing at only one storage temperature, and presents a unique nomogram for easy extrapolation. Witthaus also reports that the laws of

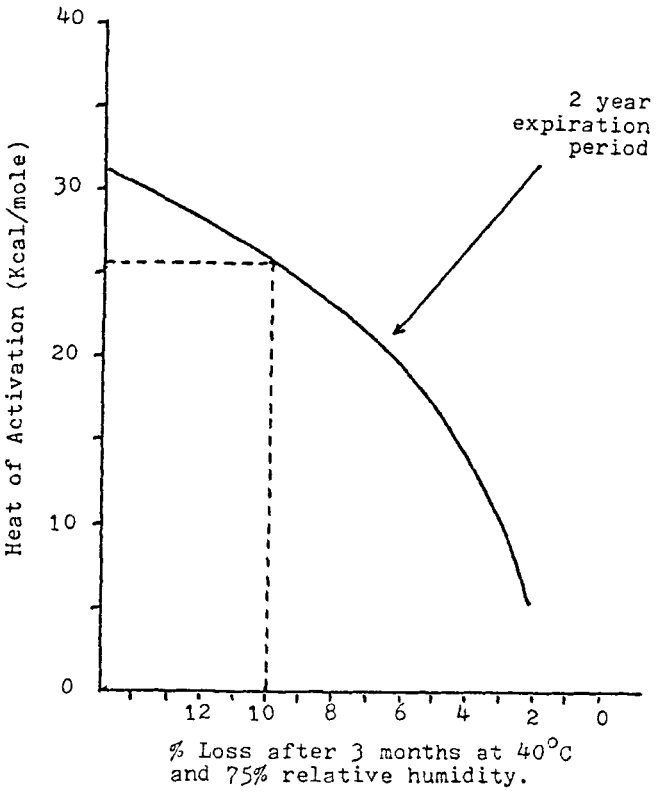

Figure 1

reaction kinetics do not apply only to liquid dosage forms, but in numerous cases can also be applied to solid and semi-liquid dosage forms.

However, I must emphasize that those conditions previously outlined for a one temperature accelerated test are only one set of many possibilities and are minimal for establishing a two year tentative expiration date. A multi-temperature study will certainly provide more information and probably a more valid estimate of product stability. The type of accelerated study chosen may require a longer test period at less harsh conditions if the product is known to degrade at high temperatures, such as soft gelatin capsules might, or if it should have a completely different pathway of chemical degradation at higher temperatures. Whichever test chosen should be, above all, reasonable. Currently, there does not appear to be justification to establish a tentative expiration date based solely upon a single point high

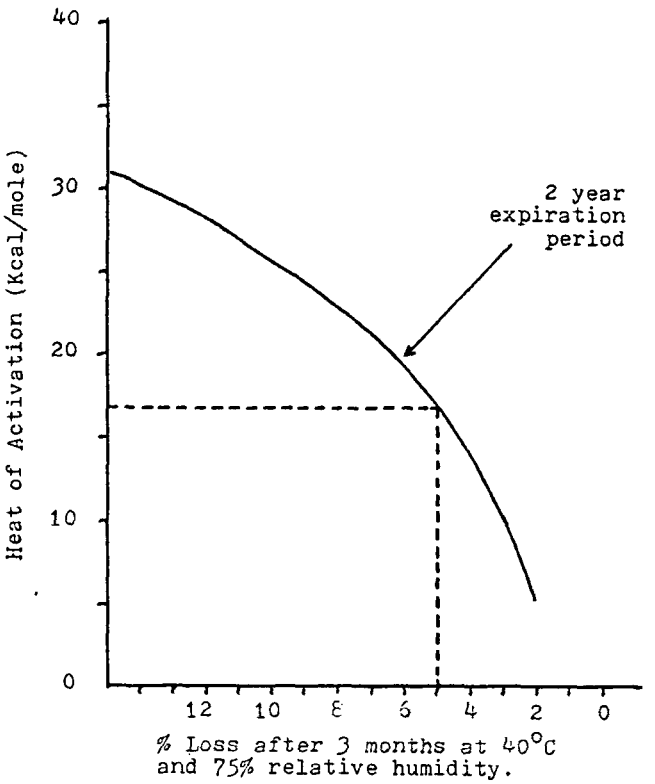

Figure 2

temperature study of only a few days. While such a test may appear valid on a plot based on the Arrhenius equation, it is nonetheless, too risky to accept such a study when one considers that a patient might receive an unsafe or ineffective drug if the prediction is in error.

The utilization of accelerated testing for establishing expiration dates must be conservatively applied, not only to the test conditions, but to the circumstances justifying such testing. While most would not consider introducing a new drug entity into the market with an expiration date based solely on an accelerated study, there are many circumstances where accelerated tests are considered adequate. Examples would be the addition of a new dosage strength to a product line; a change of formulation; a change of manufacturing process; or a change of container and/or closure.

Extending an expiration date beyond that already established might also

be accomplished through the use of accelerated studies. If one accepts the concept that an accelerated test provides sufficient information to predict a period of time a product should remain within specificaitons, one can also extend the same policy to increasing an already established expiration dating period. If a product which has been shown to meet specifications after storage at room temperature for a period of one year is now subjected to three months storage at 40°C and 75% relative humidity and still meets specifications, it seems reasonable that the product could now be labeled with a three year expiration dating period. Room temperature studies would, of course, have to be conducted to verify this tentative expiration date. It is important to again be reasonable in extrapolating an expiration dating period in this manner.

18.7 Tentative Expiration Dating

The purpose of allowing for tentative expiration dates is to permit manufacturers to market their drug products without hardship when they either offer a generic product to the marketplace or make a change in an existing product. In so doing, there seems to be little rationale for either setting a tentative expiration dating period that would be beyond what is needed by the manufacturer to be reasonably competitive, or that would be beyond that time period where market statistics have determined the product would be consumed. For these reasons, a tentative expiration dating period of two years seems to have become that usually applied, although longer periods are sometimes utilized.

18.8 Microbiological Aspects

When determining the stability of a particular product, it is important to consider not only the chemical and physical stability of the product, but also the ability of that product to maintain its microbiological quality. In so doing, it is important to monitor any preservatives in the product along with other ingredients regularly monitored for stability. While some have argued that the preservative is not an active ingredient and, therefore,

does not require monitoring, I have countered by saying that 1) there is no requirement that limits testing to active ingredients only, and 2) the preservative performs an active role in maintaining product integrity and therefore should be routinely monitored. The effectiveness of the preservative can be determined by performing the tests specified in the USP. (12)

Once effectiveness of a particular quantity of preservative for a particular product has been established by monitoring at least three batches of the product, a chemical test may be performed on subsequent batches to monitor the preservative level. In lieu of establishing effectiveness, suitable literature studies may be referenced. The chemical test has the obvious advantages of speed, economy, quantitation, and the ability to allow for reliable estimations.

Those preparations requiring control of the microbial quality that do not contain preservatives should be tested at specific intervals throughout the projected expiration dating period according to the release specification for bioburden which includes a limit for total microbial count and for the presence of *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* species, and *Pseudomonas aeruginosa* (see Microbial Limits Test of the USP). (13) In addition, it is recommended that topical preparations be tested for the absence of *Pseudomonas cepaceia*, *Aspergillus niger*, *Candida albicans*, and *Staphlococcus aureus* as well as any other topical pathogens that may be identified as potentially harmful. Simulated use tests on topical preparations packaged in jars and on ophthalmic products are desirable.

18.9 Recommended Information

In order to determine whether a firm is in compliance with GMP regulations, there must be an exchange of information from the firm to the agency so that this evaluation may be accomplished. The agency has recommended that the following information be obtained in order to evaluate a products stability.

1. A detailed description of the standard operating procedures covering the firm's overall product stability program including such items as:

a. Frequency of sampling.

b. Sample size.

c. Testing intervals.

d. Description of sample storage conditions.

e. General description of analyses and studies to be performed.

f. Parameters of acceptable analytical results.

g. Conditions which may allow deviations from standard practices.

2. Detailed description of the protocol used to study the product in question; the study may address the chemical, physical, and microbial quality of the product.

3. Description of the actual storage conditions for the batches in the study, i.e., temperature and humidity; report if actual storage conditions differ from any prescribed by the product labeling and, if so, explain rationale.

4. Copies of complete current labeling which lists storage requirements for the product.

5. Documentation which reports the following for each batch in the stability study:

a. Batch number.

b. Date of manufacture.

c. Formulation.

d. Container and closure system, including composition, light transmittance, size, and quantity of contents.

e. Date placed on stability study.

f. Dates of testing.

6. The initial release and stability test results; include all data that measures chemical, physical, and, when applicable, microbial quality of the product; include data from any accelerated study, describing storage conditions (temperature and relative humidity), storage period, dates, and results of testing.

Note: Summaries of testing are acceptable, provided actual results are reported in lieu of conclusions. For example, if pH is measured,

the test summary should report the actual value, instead of a pass or fail conclusion.

7. A statement whether stability testing has been discontinued and, if so, report the rationale for the discontinuance.
8. Copies of testing methodology; it is not necessary to supply copies of any compendial methods used, rather, cite exact references; submit copies of any method validation studies that demonstrate the precision, accuracy, reproducibility, and ruggedness of the method.
9. State whether the assay methodology is considered to be stability indicating; include scientific rationale and any supportive analytical data; state whether additional testing is performed to detect degradation products and, if so, describe the additional testing.
10. State whether there is any written statistical analysis of stability testing results; if so, submit a copy. A statistical analysis is often used to generate potency regression curves which may be useful in predicting the stability of a product.

If a firm is using different test methods as originally employed in their studies, the rationale and any appropriate data demonstrating comparability of the methods should be submitted. Similarly, if a firm does not have specific stability information required because they are extrapolating in some manner, their rationale for extrapolation and the data base from which extrapolation was made should also be submitted.

18.10 Summary

The preceding is to provide guidance to the reader on the various aspects of stability testing as outlined in the GMP regulations. The views expressed are solely those of the author and do not necessarily reflect policy and/or opinions of the Food and Drug Administration.

REFERENCES

1. Code of Federal Regulations, Title 21 - Food and Drugs, Parts 210 and 211 (1982).

2. Nyqvist, H. and Nicklasson, M., "Studies on the physical properties of tablets and tablet excipients. IV A program for accelerated light stability testing," Acta Pharm. Suec., 19, 91-98 (1982).

3. Lachman, L., Lieberman, H.A., and Kanig, J.L., The Theory and Practice of Industrial Pharmacy, 2nd ed., 181-182 and 209-210, Lea and Febiger, Philadelphia (1976).

4. Unites States Pharmacopeia, XX, System Suitability Tests, xl and 945-946 (1980).

5. United States Pharmacopeia, XX, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets, 955 (1980).

6. Kennon, L., "Use of Models in Determining Chemical Pharmaceutical Stability," J. Pharm. Sci., 53, (7), 815-818 (1964).

7. Mcleod, H.A., Pelletier, O., and Campbell, J.A., Canadian Pharm. J., March, 173 (1958).

8. Schroeter, L.C., and Higuchi, T., J. Pharm. Sci., 47, 426 (1958).

9. Yang, W. and Roy, S., "Projection of Tentative Expiry Date from One-point Accelerated Stability Testing," Drug Development and Industrial Pharmacy, 6 (6), 591-604 (1980).

10. Fung, H., Presentation at the 128th APhA Annual Meeting, St. Louis, MO, March 30, 1981.

11. Witthaus, G., "Accelerated Storage Tests: Predictive Value," Topics in Pharmaceutical Sciences, Breimer and Speiser, 275-290, Elsevier, Netherlands (1981).

12. United States Pharmacopeia, XX, Antimicrobial Preservatives - Effectiveness, 873-874 (1980).

13. United States Pharmacopeia, XX, Microbial Limit Test, 874-878 (1980).