U.S. Food and Drug Administration

Expiration Dating and Stability Testing for Human Drug Products

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ITG SUBJECT: EXPIRATION DATING AND STABILITY TESTING FOR HUMAN DRUG PRODUCTS

BACKGROUND

Publishing of 21 CFR Part 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals established requirements concerning the expiration date on a drug product and stability testing to assure the appropriateness of that date. Each drug product may be a unique article because of, for instance, differences in (1) chemical and physical properties of the active ingredients or the excipients, (2) manufacturing procedures, (3) formulations, (4) containers and closures, (5) proposed storage conditions, and (6) the stability of the article to maintain its quality or purity through the use of antioxidants or preservatives. Because of the uniqueness of each drug product, it is virtually impossible to provide one set of rules that can apply to all situations. The CGMPs were purposely written broadly to allow for such unique differences.

EXPIRATION DATING (21 CFR 211.137)

A. Absence of an Expiration Date

The absence of an expiration date on any drug product packaged after September 29, 1979, except for those drugs specifically exempt by 211.137 (e), (f), and (g), is cause to initiate regulatory action against the product and/or the responsible firm.

B. Exemptions

OTC drug products meeting the exemption of 211.137 (g) may utilize accelerated testing programs to support the requirement that they are stable for at least three years. Information obtained from old stock, not previously the subject of stability studies, may also be utilized.

C. Products Intended for Reconstitution

Any drug product intended for reconstitution and not bearing an expiration date for the unreconstituted product and another expiration date for the product after reconstitution is considered to be out of compliance with 211.137 (c). There must be separate stability studies to support each expiration date.

STABILITY TESTING (21 CFR 211.166)

A. Written Stability Testing Program

The absence of a written protocol for stability testing is cause to initiate regulatory action against the product and/or the responsible firm.

B. Supportive Stability Data

1. Number and Size of Batches

   Initial stability testing by accelerated testing may be performed on a batch smaller than the normal production size as long as the batch is produced by similar equipment as would be used for regular production.

   Generally, the placing of three initial batches into the long term stability program is considered minimal to assure batch uniformity for establishing an expiration date. Since a dosage form is a complex unit and there are continued variables in the production process, such as change in personnel, raw material lots and suppliers, and equipment, it is imperative that stability studies are not limited only to initial production batches but a portion of annual production batches be the subject of an ongoing stability program.

2. Accelerated Studies

   When accelerated stability studies are performed, one batch may be adequate in order to establish a tentative expiration date. This is acceptable

since it is not the purpose of an accelerated test to determine batch uniformity but rather to test for kinetic degradation.

The use of accelerated testing data to establish a tentative expiration dating period of greater than three years is discouraged when it is based solely on accelerated data. Combining data compiled at room temperature and at accelerated temperature is possible to justify an expiration dating period of over two years. This can be done, as an example, by taking a sample product that has been at room temperature for one year and subjecting that sample to accelerated temperature conditions. The expiration dating period used would then be the sum of that justified individually at each storage condition.

We do not believe it is reasonable to perform accelerated testing at very high temperatures for a very short time and expect to extrapolate results to a very long expiration dating period since the actual mechanism of degradation at high temperature may be different than at room temperature.

3. Test Intervals

It is commonly recommended that stability testing be performed initially, than every three months for the first year, then every six months for the second year, and then annually thereafter. However, more frequent testing near the end of the anticipated expiration date is often likely to give better information about the actual stability of the finished product. Nonetheless, testing at least annually is considered minimal for compliance with CGMPs. Some firms have chosen, for economical purposes, random dates to test all stability samples of a given product. As long as there is at least one test performed annually, this approach can be quite satisfactory.

4. Storage Conditions

If a product was stored under controlled conditions, those actual conditions (temperature and humidity) should be recorded. Merely stating that a product was stored at room temperature is not sufficient for purposes of determining stability. The USP defines controlled room temperature as being between 15 and 30 C (59 and 86 F). A product stored for stability at or near 15 C may have quite a different quality profile at its expiration date than a product stored at or near 30 C. Based on published information, it appears that 24-25 C is a reasonable reference for thermal exposure at room temperature.

Stability studies should be conducted on product stored under normal storage conditions or, preferably, under exaggerated conditions. Products liable to degradation by light or moisture should be stored either in a lighted area or under conditions of high humidity unless it can be demonstrated that the packaging will prevent deterioration by that condition of interest. For example, a product liable to degrade by light need not be stored in a lit area if it is normally packaged and stored for use in an opaque container.

5. Test Methods

While 211.166 (a) (3) merely requires that test methods be reliable, meaningful, and specific, section 211.165 (e) gives more guidance by stating that the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Section 211.194 (a) (2) further requires that all testing methods used shall be verified under actual conditions of use. Testing procedures must include a stability indicating test which will distinguish the active ingredient from any degradation products and be able to make a reliable estimate of the quantity of any degradate. The stability indicating test does not have to be the assay method used to determine product strength.

Manufacturers, who contract with analytical laboratories to perform either end product testing or stability studies, or who produce product under contract for other firms are ultimately responsible for the quality of the product and must have copies of all analytical procedures employed and the appropriate documentation to assure their validity on file. Likewise, repackers who rely on stability studies performed by the manufacturer must have copies of all analytical data necessary to support the expiration dating period.

Although specific methods are critical to determine product stability, they do not have to employ any specific technique. The use of quantitative analysis, where limits are known, such as thin layer chromatography, may be satisfactory. While many USP tests are specific for the drug or its degradates and may be used for stability testing, some USP monographs do not incorporate stability indicating tests. Additionally, it may be unreasonable to expect a manufacturer to develop specific methodology for each component of some multi-component drugs containing ingredients of botanical origin such as benzoin, Peruvian balsam or tolu balsam.

6. Container-Closure Systems

   The requirement that stability testing be performed in the same container-closure system as that in which the drug product is marketed has been subject to interpretation. The courts ruled in U.S. vs. Kaybel that when a "new drug" was repackaged, the repacker did not have to obtain pre-market approval of the repackaged product or the firm's repacking procedures. However, the repacker is subject to applicable current good manufacturing practices.

   Although stability studies were performed on the dosage unit in the original manufacturer's container, the event of placing the dosage unit into a different storage unit may and often does affect the product's shelf life. It is the policy of the Center for Drugs and Biologics to allow repacking into container-closure systems that can be demonstrated to be at least as protective or more protective than the original system without performing new stability studies prior to marketing.

   Satisfactory comparison of container-closure systems may be done by several methods, i.e., literature reference to permeation properties of different container materials; performance of moisture permeation testing; or comparing the properties of the original container-closure system to a new system by stress testing. (Stress testing refers to testing the product after storage under exaggerated conditions. This will usually involve high temperature and high humidity.)

   It is also current policy to allow firms to repackage solid dosage units from plastic containers into glass containers because glass has been shown to be a superior moisture and gas barrier. This policy does not apply to liquid drugs because of pH problems resulting from the alkaline nature of glass. Policies relating to the expiration dating of unit dose repackaged drugs may be found in Compliance Policy Guide 7132b.11. This also does not apply to repacking from bulk containers.

7. Container Sizes to be Tested

   When the same product is marketed in more than one size, e.g., bottles containing 100 tablets and bottles containing 1,000 tablets, or bottles containing 4 oz of syrup and bottles containing 16 oz of syrup, it can be demonstrated, by comparing the ratio of the surface area of the container to

the internal volume, that smaller containers have a higher ratio than larger containers. This indicates that the smallest marketed container is the most critical in terms of the container properties contributing to product degradation. Thus, moisture or oxygen permeation through a 4 oz bottle is more critical than through a 16 oz bottle of similar construction. For this reason, when studying stability of the product marketed in several sizes of similar containers, testing of the smallest container size is imperative to be in compliance with CGMPs. While we recommend that all other container sizes be subjected to stability testing, the fact that some may not is not necessarily a violation of CGMPs.

8. Preservatives

   Products formulated to contain preservatives to inhibit microbial growth should be monitored throughout their shelf life to assure the effectiveness of the preservative system. Once a minimally effective level of preservative is established, chemical testing for the preservative(s) may be performed. The preservative system should be monitored at the same stability testing times as other ingredients are monitored.

9. Bulk Drug Substances (Bulk Pharmaceutical Chemicals)

   While expiration dating is not required specifically for bulk drugs in the CGMP regulations, it is feasible and valuable to expect the manufacturer of bulk drug substances to assure that their product is stable for the intended period of use.

   A stability testing program for bulk drug substances should contain, at the minimum, the following features:

   a. The program shall be in writing.
   b. The program should include samples from at least one commercial-size batch; thereafter, one batch each year should be entered into the program.
   c. Samples should be stored in containers that approximate the market containers; if it is not practical to do so, samples may be stored in other similar containers, provided that data show that such containers will yield results comparable to those obtained with market containers.

d. Samples should be stored at room temperature; an additional sample stored at elevated temperatures or under other stress conditions may be used if it is appropriate to do so.

10. Sterility Testing

Products manufactured as sterile must maintain that quality throughout the labeled expiration dating period as long as the product is unopened and stored according to labeled instructions. The ability of the product to retain its sterile condition is a function of the container-closure system. When qualifying the container-closure system, sterility testing should be performed initially and at the end of the expiration dating period. Once any particular container-closure system can be demonstrated to maintain sterility throughout the expiration dating period, it is unnecessary to revalidate its ability to maintain sterility for other ingredients that may be placed into the same container-closure system.

Products sterilized in glass ampuls need not be subjected to sterility testing as part of the stability testing program.