CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR SUBMITTING DOCUMENTATION

FOR THE STABILITY OF HUMAN DRUGS AND BIOLOGICS

February 1987

For further information regarding the guideline please contact:

Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Research and Review
5600 Fishers Lane
Rockville, Maryland 20857
(301-443-4330)

ERRATA

Page 1, First Paragraph

Line 3: Change "Section II" to "Section III".

Page 1, Second Paragraph

Line 3: Change "Section III" to "Section IV".

Line 4: Change "Section IV" to "Section V".

Line 5: Change "Section V" to "Section VI".

Page 3, First Full Paragraph. "Approved Stability Protocol":

Line 5: Add the following: "It should be in accordance with the objectives of this guideline."

Page 41, First Full Paragraph

Line 2: Change "Sections II.A..." to "Sections III.A...."

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GUIDELINE FOR SUBMITTING DOCUMENTATION FOR THE STABILITY OF HUMAN DRUGS AND BIOLOGICS

I. INTRODUCTION

This guideline provides:

- Recommendations for the design of stability studies to establish appropriate expiration dating period(s) and product storage requirements (Section II).

- Recommendations for submission of stability information and data to the Center for Drugs and Biologics (CDB) for investigational new drugs (IND's) and biologics (Section III), new drug applications (NDA's) (Section IV), and biological product license applications (PLA's) (Section V).

The guideline is issued under 21 CFR 10.90. An applicant may rely upon the guideline in submitting documentation for the stability of human drugs and biologics, or may follow a different approach. When a different approach is chosen, a person is encouraged to discuss the matter in advance with the Food and Drug Administration (FDA) to prevent the expenditure of money and effort on preparing a submission that may later be determined to be unacceptable.

The intention is to provide a means of meeting the regulatory requirements as listed below:

IND's	21 CFR 312.23(a)(7)
NDA's	21 CFR 314.50
ANDA's	21 CFR 314.55
PLA's	21 CFR 601.2
Supplements	21 CFR 314.70

This guideline provides a means of developing expiration dating from at least three different batches of the drug product, in order to ensure a statistically acceptable level of confidence for the period proposed. It is important, however, to realize that the manufacturer is responsibile for confirming estimated expiration dating periods by continual assessment of stability properties. Such continuing confirmation of the expiration dating period should be an important consideration in the manufacturer's stability program.

II. DEFINITIONS

Accelerated Testing: Studies designed to increase the rate of chemical or physical degradation of a drug substance or drug product by using exaggerated storage conditions. The purpose is to

determine kinetic parameters, to predict the tentative expiration dating period. The term "accelerated testing" is often used synonymously with "stress testing."

Approved Stability Study Protocol: The detailed plan described in an approved NDA and applied to generate and analyze acceptable stability data in support of the expiration dating period. May also be used in developing similar data to support an extension of that dating period.

Batch: As defined under 21 CFR 210.3(b)(2), "'Batch' means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture".

Bulk Drug Substance: The pharmacologically active component of a drug product before formulation.

Commitment: A signed statement by an applicant of an NDA, an ANDA, or a PIA to conduct (or complete) prescribed studies on commercial production lots after approval of an application. A commitment to obtain data may be accepted in lieu of the data themselves when available data do not cover the full expiration dating period for the specific product/container-closure, but there are sufficient

supporting data to predict a favorable outcome with a high degree of confidence (e.g., when an NDA is approved with stability data available only from experimental or pilot lots (not production lots), or when a supplement is approved with data that do not cover the full expiration dating period). A commitment constitutes an agreement to:

- Conduct or complete the desired studies.

- Submit results periodically, as specified by the FDA.

- Withdraw from the market any lots found to fall outside the approved specifications for the drug product. If the applicant has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the applicant should immediately discuss it with the reviewing division and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug produce is required to be reported, as required under 21 CFR 314.81(b)(1)(ii).

Drug Product: As defined under 21 CFR 210.3(b)(4), "drug product" means a finished dosage form (e.g., tablet, capsule, solution, etc.) that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients.

Expiration Date: The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specifications. If the expiration date includes only a month and year, it is expected that the product will meet specifications through the last day of the month.

Expiration Dating Period: The interval that a drug product is expected to remain within the approved specifications after manufacture. The expiration dating period is used to establish the expiration date of individual batches. It may be extended in an annual report only if the criteria set forth in the approved stability study protocol are met in obtaining the supporting data. Otherwise, a supplement requiring FDA approval will be necessary before the change is made. (21 CFR 314.70(b)(2)(ix))

Lot: As defined under 21 CFR 210.3(b)(10): "'Lot' means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specific limits."

Primary Stability Data: Data on the drug product stored in the proposed container-closure for marketing under storage conditions that support the proposed expiration date.

Random Sample: A selection of units chosen from a larger population of such units so that the probability of inclusion of any given unit in the sample is defined. In a simple random sample each unit has equal chance of being included. Random samples are usually chosen with the aid of tables of random numbers found in many statistical texts.

Stability-Indicating Methodology: Quantitative analytical methods that are based on the characteristic structural, chemical, or biological properties of each active ingredient of a drug product and that will distinguish each active ingredient from its degradation products so that the active ingredient content can be accurately measured.

Stability: The capacity of a drug product to remain within specifications established to ensure its identity, strength, quality, and purity.

Strength: A quantitative measure of active ingredient, as well as other ingredients requiring quantitation, such as alcohol and preservatives. (See 21 CFR 210.3(b)(16).)

Stress Testing: See "Accelerated Testing".

Supportive Stability Data: Data other than primary stability data, such as stability data on investigational formulations not proposed for marketing, accelerated studies on the bulk drug substance, published stability data, references to other submissions on file with the agency with appropriate letters of authorization, accelerated studies on the proposed drug product for marketing, information regarding test results on containers, and other scientific rationale that supports the proposed expiration dating period and storage conditions.

Tentative Expiration Dating Period: A provisional expiration dating period determined by projecting results from less than full-term data (such as accelerated studies) using the drug product to be marketed in the proposed container-closure.

III. DESIGN AND INTERPRETATION OF STABILITY STUDIES

The design of the stability protocol should include methodology for determining the stability of the bulk drug substance and drug product and the statistics relating to sampling and data analysis.

The stability-indicating methodology should be validated by the manufacturer (and the accuracy and precision established) and described in sufficient detail to permit validation by FDA laboratories (Ref. 1).

The revision of the NDA regulations in 21 CFR Section 314.70(d)(5) should direct more attention to the importance of properly designing a stability study, because only by submitting full shelf-life data from an approved stability protocol can an applicant extend an expiration date without supplemental application.

A. Bulk Drug Substance Profile

Stability information on the drug substance before formulation is valuable in identifying characteristics of the intact molecule that can change under defined storage conditions. When such labile characteristics are found, it is advisable to include those storage conditions in the stability study protocols designed for all drug products of the drug substance. For the purpose of this guideline, studies to define the Drug Substance Stability Profile need be conducted only once for each new drug substance produced by the same manufacturing process. These studies may also be useful in establishing packaging requirements, storage conditions, and an expiration dating period where required (antibiotics).

Stability studies on the bulk drug substance are needed when adequate stability information is unavailable either from prior studies or from the literature (Ref. 2). A program for the stability assessment might include storage at ambient temperature and under stressed conditions. Stress-testing

conditions ordinarily include temperature (e.g., 5°, 50°, and 75°C); humidity, where appropriate (e.g., 75 percent or greater), and exposure to various wavelengths of electromagnetic radiation (e.g., 190-780 nanometers, i.e., ultraviolet and visible ranges) (Refs. 3-6), preferably in open containers, where applicable.

It is also suggested that the following conditions be evaluated in stability studies on solutions or suspensions of the bulk drug substances:

- Acidic and alkaline pH.

- High oxygen atmosphere.

- The presence of added substances under consideration for product formulation.

It is important to detect, isolate, and identify degradation products. Degradation products should be quantified and the reaction kinetics established, if practicable.

B. Drug Products

Stability studies on samples prepared under conditions simulating production of the finished drug product, and contained in the market package stored at the temperature stated

on the label, are required to support assignment of an expiration date. Stress testing of the drug product is frequently used to identify potential problems that may be encountered during storage and transportation and to provide an estimate of the expiration-dating period. Other special studies may be of value for specific drug products (see III.B.6.a-m, below).

When designing stability studies, the following should be considered:

1. Container-Closure

   Stability data should be developed for each type of immediate container-closure proposed for marketing the drug product that differs in composition from other container closures or design (e.g., wall thickness for plastic container, torque, etc.), including child-resistant and tamper-resistant closures, regardless of similarities in cap liners. Physicians' samples should also be included in the stability studies if their container-closure is different from the market package. The possibility of interaction between drug and container-closure and the introduction of leachables into drug formulations during storage should be assessed by sensitive procedures, quantitative when

practicable. This is necessary even if the container-closure meets suitability tests, such as those outlined in the United States Pharmacopeia (U.S.P.) for plastic containers and rubber or plastic closures.

For most solid-dosage drug products, stability data need only be obtained for the smallest and the largest container-closure to be marketed, provided that any intermediate size container-closure is of identical composition. Stability data should, however, be submitted for all sizes of multiple-unit containers such as parenterals, aerosols, etc. (see separate entries under III.B.6 for details).

Where package container sealant integrity is to be assessed in the study protocol, higher than 75 percent relative humidity at 37°C may be appropriate to stress its adhesive properties (e.g., blister units and strip packages).

2. Extreme Temperature Fluctuations

A study of the effects of temperature fluctuation as appropriate for the shipping and storage conditions of the drug products should be considered (i.e., the packaged drug product should be cycled through temperature conditions that simulate the changes that may be encountered once the drug product is in distribution).

3. Storage Temperatures

The actual storage temperatures (numerical) used during stability studies should be specified.

4. Microbial Quality

Drug products containing preservatives to control microbial contamination should have the preservative content monitored at least at the beginning and end of the projected expiration dating period of the drug product. This may be accomplished by performing microbial challenge tests (e.g., Antimicrobial Preservatives Effectiveness test of the U.S.P., which is applicable to unopened containers) or by performing chemical assays for the preservative. When the lower specification level of preservative needed to achieve effective microbial control has been determined, chemical assays may be adequate provided that periodic challenge tests are performed (Ref. 7). It is particularly important to consider the adequacy of the preservative system under conditions of use for multiple-use containers (e.g., parenterals, syrups, suspensions, etc.) (Ref. 8).

Nonsterile preparations that require control of the microbial quality and that do not contain preservatives should be tested at specific intervals throughout the

projected expiration dating period according to the release specification for bioburden (e.g., Microbial Limits Tests of the U.S.P.). In addition, it is recommended that topical preparations also be tested for the presence of topical pathogens that may be identified as potentially harmful (e.g., Pseudomonas cepacia, Aspergillus niger, and Candida albicans). Simulated use tests on topical preparations packaged in jars and on ophthalmics are desirable.

5. Degradation Products

When degradation products are detected, the following information about them should be submitted when available:

- Identity and chemical structure.

- Cross-reference to any available information about biological effect and significance at the concentrations likely to be encountered.

- Procedure for isolation and purification.

- Mechanism of formation, including order of reaction (see III.C.1.c., below).

- Physical and chemical properties.

- Specifications and directions for testing for their presence at the levels or concentrations expected to be present.

- Indication of pharmacological action or inaction.

6. Generally Acceptable Design Considerations for Specific Drug Products

a. Tablets: A stability study should include tests for the following characteristics of the tablet: Appearance, friability, hardness, color, odor, moisture, strength, and dissolution.

b. Capsules: A stability study should include tests for the following characteristics: Strength, moisture, color, appearance, shape, brittleness, and dissolution. [For soft gelatin capsules, the fill medium should be examined for precipitate, cloudiness, and pH.]

c. Emulsions: The following characteristics should be examined: Appearance (such as phase separation), color, odor, pH, viscosity, and strength. Storage on the side

or inverted is suggested for assessment of the closure systems. It is recommended that a heating/cooling cycle be employed (e.g., between 4° and 45°C) (Refs. 9 and 10).

d. Oral solutions and suspensions: The following characteristics should be examined: Appearance (precipitate, cloudiness), strength, pH, color, odor, redispersibility, dissolution (suspensions), and clarity (solutions). Liquids and suspensions should be stored on their side or inverted in order to determine whether contact of the drug product with the closure system affects product integrity.

After storage, samples of suspensions should be prepared for assay in according to the recommended labeling.

e. Oral powders: Most oral powders are marketed for reconstitution prior to administration. The following characteristics of the powder should be examined: Appearance, strength, color, odor, and moisture. The reconstituted product should be prepared according to the recommended labeling. Specific characteristics to be examined on the reconstituted material should include: Appearance, pH, dispersibility, and strength throughout the recommended storage period.

f. Metered-dose inhalation aerosols: Characteristics that should be examined in a stability study for all container-closure sizes include the following: Strength, delivered dose per actuation, number of (metered) doses, color, clarity (solutions), particle size distribution (suspensions), loss of propellant, pressure, valve corrosion, and spray pattern (Ref. 11).

Because the container contents are under pressure, filled containers must be checked for weight loss over the expiration dating period. For suspensions, aggregate (or solvate) formation may lead to clogged valves or to the delivery of a pharmacologically inactive dose. Corrosion of the metering valve or gasket deterioration may adversely affect the delivery of the correct amount of drug substance.

If the drug product is intended for use in the respiratory system, it is important to confirm that the initial release specifications are maintained to assure the absence of pathogenic organisms (e.g., Staphylococcus aureus, Pseudomonas aeroginosa, Escherichia coli, and Salmonella species) and the total microbial limit per cannister.

g. Topical and ophthalmic preparations: Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, and nonmetered aerosols for application to the skin. For stability studies of topical ointments, creams, lotions, solutions, and gels, the following characteristics should be examined, as appropriate to the

drug product: Appearance, clarity, color, homogeneity, odor, pH, resuspendibility (lotions), consistency, particle size distribution, strength, and weight loss (plastic containers).

Ointments, pastes, and creams, in containers larger than 3.5 grams, should be assayed by sampling at the surface, middle, and bottom of the container. In addition, tubes should be sampled near the crimp.

Evaluation of nonmetered aerosols should include the following: Appearance, odor, strength, pressure, weight loss, net weight dispensed, delivery rate, and spray pattern.

Evaluation of ophthalmic preparations (e.g., creams, ointments, solutions, and suspensions) should include the following as appropriate to the drug product: Appearance, odor, consistency, pH, resuspendibility, particle size, homogeneity (suspensions, creams, and ointments), strength, and sterility.

h. Small-volume parenterals (SVP's): SVP's include an extremely wide range of preparations and container-closures, all of which should be included in the stability study. Evaluation of these drug products should include at least the following: Strength, appearance, color, particulate matter, pH, sterility, and pyrogenicity (at reasonable intervals). Stability studies on powder products should demonstrate that the residual moisture content remains within acceptable limits and that the product is stable throughout the recommended storage period.

The stability of reconstituted products should also be determined after they are constituted according to the recommended labeling. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the constituted drug product,

stored under condition(s) recommended in labeling, should include: Appearance, odor, color, pH, strength, dispersibility, and particulate matter.

Continued assurance of sterility for all sterile products may be assessed by a variety of means, including evaluation of the container-closure integrity by appropriate challenge test(s), testing for preservatives (if present), and/or sterility testing.

For terminally sterilized drug products, a specification for maximum process parameters should be provided. Stability studies should evaluate and support the adequacy of the maximum release specification for process lethality (e.g., F_o, Mrads, etc.).

Parenterals (except ampules) should be stored inverted or on their sides in order to determine, by comparison, whether contact of the drug product or solvent with the closure system affects product integrity or results in leaching of chemical substances from the closure material.

i. Large-volume parenterals (LVP's): Stability tests for LVP's are similar to those for SVP's. A minimum evaluation should include the following: Strength, appearance, color, clarity, particulate matter (U.S.P. or equivalent), pH, volume (plastic containers), extractables (plastic containers), sterility, and pyrogenicity (at reasonable intervals).

Continued assurance of sterility for all sterile products may be assessed by a variety of means, including evaluation of the container-closure integrity by appropriate challenge test(s), by testing for preservatives (if present), or by sterility testing.

These products should be stored with some inverted and some on their sides in order to determine whether contact of the drug product or solvent with the container-closure system affects product integrity, or results in leaching of chemical substances from the container-closure material.

j. Suppositories: Suppositories should be evaluated for strength, softening range, appearance, and dissolution. The effect of aging may also be observed from a hardening of the suppository and a polymorphic

transformation of the drug substance; therefore, control and stability testing should include dissolution time at 37^{o} C.

k. Drug additive: For any drug product that is intended for use as an additive to another drug product, the possibility of incompatabilities exists. In such cases, the drug product labeled to be administered by addition to another drug product (e.g., parenterals, aerosols) should be studied for stability and compatability in admixture with the other drug product.

A suggested stability protocol should provide for tests to be conducted at 0-, 6-to-8-, and 24-hour intervals, or as appropriate over the intended use period. These should include:

- Assay of the drug product and additive.
- pH (especially for unbuffered LVP's), color, clarity.
- Particulate matter.
- Interaction with the container.

1. Intrauterine devices and vaginal devices regulated as drugs

Stability testing for intrauterine devices (IUD's) should include the following tests: Deflection of horizontal arms or other parts of the frame if it is not a T-shaped device (frame memory), tensile strength of the withdrawal string, and integrity of the package (i.e., seal strength of the pouch and sterility of the device).

If the device contains a drug substance reservoir from which drug substance diffuses through a controlled-release membrane, it should be tested for total drug substance content, decomposition products, and in vitro drug product release rate in addition to the above tests.

Vaginal devices such as a doughnut-shaped silastic or other polymeric matrix containing a drug product uniformly dispersed throughout the matrix must be checked for in vitro drug product release rate and extraneous extractable substances to establish stability and drug product compatibility with the matrix.

m. Biological products: In addition to other parameters described for specific drug products, it is required for biological products that potency be a measure of biological activity. Generally, the official potency test (21 CFR Parts 600-680), or the potency test described in the manufacturer's approved license application for a given product, will be adequate for potency determination.

C. Statistical Considerations

Under 21 CFR 314.70(d)(5), a new drug applicant may take certain actions on the basis of an approved stability study protocol, such as extending an expiration dating period based on full shelf-life data without prior approval of a supplemental application by including the change in the next annual report under § 314.81(b)(2). A stability study protocol must describe not only how the stability study is to be designed and carried out, but also the statistical methods to be used in analyzing the data. An acceptable approach is described in part 2, below. If the sponsor wishes to use an alternative statistical procedure, it must be described in the stability study protocol. Part 1 of this section describes specific design features of stability studies that are pertinent to the statistical analysis.

1. Design Considerations for Long-Term Studies Under Ambient Conditions (Nonaccelerated Data)

The design of a stability study is intended to establish, based on testing a limited number of batches of a drug product, an expiration dating period applicable to all future batches of the drug product manufactured under similar circumstances. This approach assumes that inferences drawn from this small group of tested batches extend to all future batches. Tested batches must, therefore, be representative in all respects (e.g., formulation, container-closure system, manufacturing process, age of bulk material, etc.) of the population of all production batches of that drug product and conform with all quality specifications.

The design of a stability study should take into consideration the variability of individual dosage units, of containers within a batch, and of batches, in order to ensure that the resulting data for each batch are truly representative of the batch as a whole and to quantify the variability from batch to batch. The degree of variability affects the confidence one might have in the ability of a future batch to remain within specifications until its expiration date.

a. Batch sampling considerations: Ideally, the batches selected for stability studies should constitute a random sample from the population of production batches. In practice, the batches tested to establish the expiration dating period are usually the first batches produced, but sometimes they may be research or pilot scale batches. If research or pilot scale batches are used, they should have the same characteristics as production scale batches, including the relative proportions of active and inactive ingredients. It is possible that future changes in the production process will result in the obsolescence of the initial stability study conclusions.

At least three batches and preferably more should be tested to allow for some estimate of batch-to-batch variability and to test the hypothesis that a single expiration dating period for all batches is justifiable.

Testing of a single batch does not permit assessment of batch-to-batch variability, and testing of two batches provides an unreliable estimate. Although it is true that more data (batches) result in a more precise estimate, practical considerations prevent unlimited

collection of data. The specification that at least three batches be tested is a minimum requirement representing a compromise between statistical and practical considerations.

b. Container-closure and drug product sampling considerations: Selection of containers (bottles, packages, vials, etc.) from the batches chosen for inclusion in the stability study should be carried out so as to ensure that the samples chosen represent the batch as a whole. This may be accomplished by taking a random sample of containers from the finished batch, by using a plan whereby at a random starting point every nth container is taken from the assembly line (n is chosen so the sample is spread over the whole batch), or by some other plan designed to ensure an unbiased selection.

Samples to be assayed at a given sampling time are to be taken from previously unopened containers. For this reason, at least as many containers must be sampled as the number of sampling times in the stability study. In any case, sampling of at least two containers for each sampling time is encouraged.

As a rule, dosage units from a given container should be sampled randomly, with each dosage unit having an equal chance to be included in the sample. If it is believed that the individual units entered the container randomly, then sampling of the units at the opening of the container is acceptable. With large containers, because dosage units near the cap of a bottle may have different stability properties than dosage units in other parts of the container, it may be desirable to sample dosage units from all parts of the container. (For dosage units sampled in this fashion, the location within the container from which they were taken should be identified and this information included with the results.)

Composites may be assayed instead of individual units. If more than one container is sampled at a given sampling time, an equal number of units from each container may be combined into the composite. It is suggested that the same type of composite be used throughout the stability study, e.g., if 20-tablet composites are tested initially, then 20-tablet composites should be used throughout. If it is desired

to have a larger sample at a given sampling time, replicated 20-tablet composities would be assayed, not a single assay of a composite made from more than 20 tablets.

If composites are used, their makeup should be described in the stability study report.

c. Sampling-time considerations: The sample times should be chosen so that any degradation can be adequately characterized (i.e., at a sufficient frequency to determine with reasonable assurance the nature of the degradation curve). Usually, the relationship can be adequately represented by a linear, quadratic, or cubic function on an arithmetic or a logarithmic scale (Section III.B.6).

Stability testing generally may be done at 3-month intervals during the first year, 6-month intervals during the second, and yearly thereafter. For drug products predicted to degrade rapidly (e.g., certain radiopharmaceuticals), more frequent sampling is necessary.

The degradation curve is estimated most precisely (in terms of the width of the confidence intervals about the estimated curve, as illustrated in Figure 1) around the average of the sampling times included in the study. Therefore, testing an increased number of replicates at the later sampling times, particularly the latest sampling time, is encouraged, because this will increase the average sampling time toward the desired expiration dating period.

2. Data Analysis and Interpretation; Long-Term Studies

The methods described in this section are used to establish, with a high degree of confidence, an expiration dating period during which the average drug product characteristic (e.g., strength) of the batch will remain within specifications. This expiration dating period should be applicable to all future batches produced by the manufacturing process for the drug product. It is not sufficient that a proposed expiration dating period ensure that the process average is within specifications, if a substantial number of individual batch averages are out of specifications at the end of the proposed expiration dating period.

If an applicant chose an expiration dating period to ensure that the characteristics of a large proportion of the individual dosage units are within specifications, different statistical methods than those proposed below would be needed. For example, see Easterling (Ref. 12). Also, it would be necessary to test individual units rather than composites. However, as noted before, the following represents an acceptable approach.

a. Determining the allowable expiration dating period for an individual batch: The time during which a batch may be expected to remain within specifications depends not only on the degradation rate, but also on the initial average value for the batch. Thus any information on the initial value for the batch, such as the results of release testing on that batch, is relevant to the determination of the allowable expiration dating period and should be included in the stability study report. Also, percent of label claim, not percent of initial average value, is the variable of interest.

When establishing the expiration dating period for an individual batch, support is obtained from the observed pattern of degradation for the quantitative drug product characteristic under study (e.g., strength) and to the

precision by which it is estimated. An acceptable approach for drug characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided lower confidence limit (sometimes called the 95% lower confidence bound) for the mean degradation curve intersects the acceptable lower specification limit.

Carstensen and Nelson (Ref. 13) proposed an approach equally acceptable to this, and the 95% lower confidence limit for the mean is described in their paper and is illustrated in their Figure 1, labeled Roman Numeral I. Note, however, that Carstensen and Nelson proposed that the expiration dating period be determined on the basis of a different curve (the so-called "prediction limit," labeled Roman Numeral II in their Figure 1) than is presented here. In the example shown in our Figure 1 (where the lower specification limit is assumed to be 90% of label claim) an expiration dating period of four years would be granted. For drug product characteristics expected to increase with time (e.g., there may be an upper limit on the amount of certain degradation products), the 95% one-sided upper confidence limit for the mean would be used.

For drug product characteristics with both an upper and a lower specification limit, there may be special cases where it would be appropriate to use the two-sided 95% confidence limits. As an example, suppose the drug characteristic of interest was concentration of unchanged active ingredient for a solution. Chemical degradation of the active ingredient would decrease the concentration. On the other hand, evaporation of the solvent (possibly resulting from the characteristics of the closure) would increase the concentration. Since both possibilities must be allowed for, two-sided confidence limits would be appropriate. (If both mechanisms were acting, however, the concentration might decrease initially and then increase. In this case, the degradation pattern would not be linear and more complicated statistical methods would be needed.)

If the approach of this section is used, we may be 95% confident that the average drug product characteristic (e.g., strength) of the dosage units in the batch is within specifications up to the end of the expiration dating period. It is not acceptable to determine the allowable expiration dating period by determining where the fitted least-squares line intersects the appropriate specification limit. This approach is as likely to

overestimate the expiration dating period as to underestimate it (i.e., we may only be 50% confident that the batch average is within specifications at expiration if the fitted least-squares line is used).

The statistical assumptions underlying the procedures described above (e.g., the assumption that the variability of the individual units from the batch average remains constant over the several sampling times) are well known and have been discussed in numerous statistical texts. The above procedures will remain valid even when these assumptions are mildly violated. If there is evidence of severe violation of the assumptions in the data, an alternate approach may be necessary to accomplish the objective of determining an allowable expiration dating period with a high degree of confidence that the period does not overestimate the true time during which the drug product remains within specifications.

There may be cases where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested expiration dating period will be confirmed. Under these circumstances it would not be necessary to go through

the formal calculations involved in the above analysis. However, this case is the exception rather than the rule, and the final judgment on whether the calculations are necessary lies with the reviewers in the CDB. Consequently, failure to include the results of the analyses described above could result in a delay of the stability review, if the reviewers feel that the calculations are needed. Therefore, it is recommended that the analyses be carried out routinely.

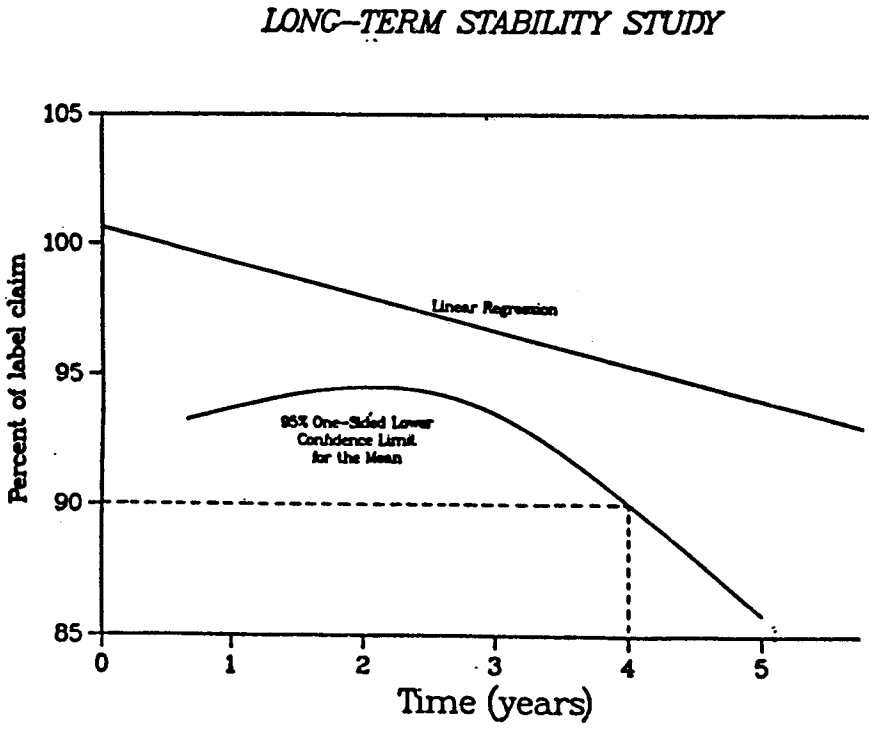

Figure 1

b. Determining the expiration dating period based on the information from all of the batches: If batch-to-batch variability is small (i.e., the relationship between the drug product characteristic of interest; e.g., strength and time is essentially the same from batch to batch), it would be advantageous to combine the data into one overall estimate. Combining the data should be supported by preliminary testing of batch similarity. The similarity of the degradation curves for each batch tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level of significance of the tests should be chosen so that the decision to combine is made only if there is strong evidence in favor of combining. Bancroft and his co-workers (Ref. 14) have recommended a level of significance of 0.25 for preliminary statistical tests similar to this. If the tests for equality of slopes and for equality of intercepts do not result in rejection at a level of significance of 0.25, the data from the batches would be pooled. If these tests resulted in p-values less than 0.25, a judgment would be made by the CDB reviewers as to whether pooling would be permitted.

If the preliminary statistical test rejects the hypothesis of batch similarity because of unequal initial intercept values, it may still be possible to establish that the lines are parallel, i.e., the slopes are equal), and in this case the data may be combined for purpose of estimating the common slope. The individual allowable expiration dating period for each batch in the stability study may then be determined by considering the initial values, using appropriate statistical methodology. If data from several batches may be combined, it is advantageous to include as many batches as feasible, because confidence limits about the estimated degradation curve will become narrower as the number of batches increases, usually resulting in a longer allowable expiration dating period.

If it is inappropriate to combine data from several batches, the overall expiration dating period may depend on the minimum time a batch may be expected to remain within acceptable limits.

3. Precautions To Be Observed in Extrapolation Beyond the Actual Data Period

The statistical methods for determining an expiration dating period beyond the range of storage times actually observed are the same as for determining an expiration period within

the observed range. However, the a priori correctness of the assumed pattern of degradation as a function of time is crucial in the case of extrapolation beyond the observed range.

When estimating an assumed degradation line or curve over the observed range of data, the data themselves provide a check on the correctness of the assumed relationship, and statistical methods may be available to test the goodness of fit of the data to the assumed degradation line or curve. No such internal check is available beyond the range of observed data.

As an example, suppose it has been assumed that the relationship between log strength and time is a straight line, but in fact the true relationship is a curve. It may be that over the range of the observed data, the true curve is close enough to a straight line so that no serious error is made by approximating the degradation relationship as a straight line. However, between the last observed data points and the estimated expiration time, the true curve may diverge from a straight line enough to have an important effect on the estimated expiration time.

For extrapolation beyond the observed range to be valid, the assumed degradation relationship must continue to apply through the estimated expiration dating period. Thus, an expiration dating period granted on the basis of extrapolation should always be verified by actual stability data up to the granted expiration time as soon as these data become available.

D. Alternate Stability Study Protocol

If for any stated reason the approach proposed in these guidelines is not suitable for the new drug or biological product under development, a different stability study protocol should be designed by the sponsor during clinical phases of investigation (Section III.C.1.). The sponsor should ensure that the stability protocol is acceptable to the CDB reviewers.

IV. INVESTIGATIONAL NEW DRUGS (IND's)

Studies conducted during development of a drug or biological product do not necessarily follow a rigid separation into Phases 1, 2, and 3, but the following is presented as a general IND development sequence that is intended to provide guidance for the development of product stability information during the investigational phases:

A. IND Phase 1

The stability characteristics of the bulk drug substance should be determined at the earliest possible time to support conditions of use of the bulk drug in toxicity studies (i.e., pre-IND studies, mixed with feed, etc.) and the stability of the drug substance in the initial formulations proposed for use in clinical pharmacological studies. This information should be included in the initial IND submission to FDA. Required stability information would be limited to that needed to demonstrate that the clinical product would be stable for the duration of the investigation. If necessary, additional data may be submitted as they become available during the course of the clinical study.

B. IND Phase 2

Stability studies on the investigational formulations should be well underway by the end of Phase 2.

Drug product or biological formulations developed during Phase 2 (as well as Phase 3) should be based upon the stability information developed from studies on the bulk drug substance or on the stability of formulations prepared in experimental

studies. The objectives of stability testing during Phases 1 and 2 are (a) to evaluate the stability of the investigational formulations used in the clinical trials and (b) to obtain the additional information needed to develop a final formulation (e.g., compatibility studies of potential interactive effects between the drug substance(s) and other components of the system). This information should be summarized and submitted to the IND when available.

C. IND Phase 3

The emphasis in stability testing during Phase 3 is on final formulations in their probable market packaging, on expiration dating, and on the study of degradation products when encountered. Studies to support the proposed expiration dating period should be completed, where possible, during Phase 3 for inclusion in the initial NDA, or in the PLA for biological products.

V. NEW DRUG APPLICATIONS (NDA's)

A. Original Submissions

Ordinarily, an original NDA submission should contain primary stability data that, when subjected to appropriate statistical

analysis (Figure 1), support the proposed expiration dating period. Also, other supportive stability data must clearly substantiate the time period assigned and the proposed storage conditions for labeling. This must be accompanied by the standard commitment to continue the stability study. (See "Commitment" in Section II.) As a condition for approval, it is expected that samples of the first three commercial production lots will be placed in the stability program for the full length of the expiration dating period for confirmation of the dating period assigned.

A full report on stability of the bulk drug substance should provide information outlined in Sections II.A and III.B.5 of the guidelines on general stability characteristics and degradation products.

Stability studies conducted for all formulations used during clinical investigations should be summarized as described in the introductory paragraph of Section III, in paragraphs B and C of that section, and in section VII of these guidelines.

The lots used for stability testing should comply <u>fully</u> with proposed specifications for the product in its market package. Studies to support an expiration dating period, under defined

storage conditions using several lots representative of the product to be marketed, should have been started as early as possible prior to the NDA.

Because a reviewer cannot make any comparisons with data contained in another application, stability data submitted must be complete within themselves.

If an alternate facility is contemplated prior to approval of an NDA, refer to Section V.D.3.

B. Computation of Expiration Date

The computation of the expiration date of the new drug production lot in its market package should begin at the time of quality control release of that lot, and the date of such release should generally not exceed 30 days from the production date, regardless of the packaging date.

If the production lot contains reprocessed material, the expiration dating period should be computed from the date of manufacture of the oldest reprocessed lot that was made to conform to the quality standards for identity, strength, quality, and purity specified in the NDA.

In general, proper statistical analysis of long-term stability data collected, as recommended in Section III C.1.a, and as exemplified in Figure 1, must support at least a 1-year expiration period.

C. Abbreviated New Drug Applications (ANDA's)

For drug products that have been approved for marketing under an ANDA, information such as stress testing, references to publications or other sources that describe the stability profile of the drug substance, and comparative stability data for the proposed drug product and of the innovator's drug product (especially when the comparative data are utilized in bioavailability/bioequivalence studies) is acceptable.

In the absence of sufficient data at the proposed storage condition, stress testing will be accepted for the grant of a tentative expiration dating period, provided adequate information concerning stability of the drug substance has been submitted. The recommended stress testing conditions are:

- 40°C, or as appropriate for a particular drug product.
- 75 percent relative humidity (where appropriate).

Samples should be analyzed initially and at 1, 2, and 3 months. The parameters described under Section III.B. should be

considered when collecting stability data for various drug products. Available long-term stability data should be included and reported as outlined in Section VII of the guideline.

If the results are satisfactory, a tentative expiration dating period of up to 24 months may be granted.

When an alternate facility is contemplated prior to approval of an ANDA, refer to Section V.D.3.

The submission should also include the following commitments:

1. The first three commercial production lots of the product will be placed on stability testing as specified in Section II. C.6. Testing at the recommended storage conditions should be done, initially, at 3, 6, 9, 12, 18, and 24 months, and yearly thereafter until the desired expiration date of the product is reached. If more than one package size is marketed, the first three commercial production lots of the smallest and the largest size should be tested. Also, if more than one container-closure is used for a particular size, stability data in each container-closure should be submitted. Yearly, thereafter, at least one production batch should be added to the stability program.

2. Results will be submitted in the next periodic report or as specified by the FDA.

3. Any lots found to fall outside of the approved specifications for the drug product may be withdrawn from the market. Deviations that do not affect the safety and efficacy of the product will be promptly discussed between the applicant and the reviewing division and must be reported to FDA under 21 CFR 314.81(b)(1)(ii). (Also see "Commitment" Definition.)

D. SUPPLEMENTS TO NEW DRUG APPLICATIONS

A supplement may be classified under several categories as indicated below:

1. Changes in Formulation, Supplier, and Container-Closure

A supplement that proposes a change in the drug product's formulation, in the supplier of a drug substance, or in the container-closure for a marketed drug product will usually require the development of data to show that this change does not adversely affect stability. Usually, accelerated data demonstrating comparability with the previously approved drug product, plus the standard commitment to continue the stability study, will suffice. For significant

changes of products known to be relatively unstable, 6 months' data at the normal recommended storage temperature, as well as the data from accelerated conditions, may also be required.

If the data give no reason to believe that the proposed change will alter the stability of the product, the previously approved expiration dating period may be used.

2. Interchangeability of Polyethylene Containers

A special case is the interchangeability of polyethylene containers for capsules and tablets that meet standards and tests described in the U.S.P. In this instance, a supplement may be approved with no advance stability data, provided there is a commitment to do the stability testing in accordance with the previously approved stability study protocol or as specified by FDA.

3. New Manufacturing Facilities

For a change limited to a new manufacturing facility for the identical drug product using similar equipment, 3 months' accelerated data may be needed, depending on the nature of the product, the process involved, and the stability data previously generated. A commitment should be made to conduct stability studies on at least the first three

commercial production lots based on the approved stability study protocol. Ordinarily, the already approved expiration dating period may be used under these circumstances.

4. Reprocessed Material

A supplement providing for the use of reprocessed material should include data to demonstrate that the reprocessed product has identity, strength, quality, and purity comparable to that approved in the NDA for the designated expiration dating period. Also, the standard commitment to continue the stability study should be submitted.

5. New Container Fabricator

When a new plastic container fabricator is proposed, with no change in materials or specifications, the applicant should have full specifications for the approved container to supply to the new fabricator. The new fabricator should submit manufacturing information to the applicant (or directly to FDA), and should agree to inform the drug product manufacturer immediately of any change in resin designation or supplier. The applicant should provide the standard commitment to initiate stability studies on at least the first three commercial production lots packaged in

the container from the new fabricator. Under these circumstances, accelerated or preliminary stability data are not required, and the already approved expiration dating period may be used.

VI. PRODUCT LICENSE APPLICATION FOR BIOLOGICAL PRODUCTS (PLA's)

A. General Guidelines for Biological Product Stability Studies

The components of biological products are usually protein derivatives or other organic substances. Such substances are usually heat sensitive and require refrigeration or freezing to protect the potency of the product. Therefore, the methodologies and statistical analyses used for determining the stability characteristics and expiration dating period for drug products are not necessarily applicable to biological drug products.

Because of the complexity and variety of the composition of biological products, requirements for determining their stability may differ markedly among different types of products.

Documentation of biological product stability is required for all new biological products and, when significant changes are made to the composition or to the container-closure, for currently approved biologicals. The descriptions that follow offer guidance regarding when stability data are required for

biologicals. All proposals and submissions related to biological product stability should either accompany the product license application in an original submission for licensure or be submitted as an amendment to an existing product license application. Each submission will be considered on an individual basis depending on the composition and characteristics of the product.

B. Original Submission

1. Studies Submitted with Application

Studies to support the expiration dating period of a biological product using at least three lots representative of the product to be marketed under defined storage conditions should be submitted at the time of license application filing. These lots should comply fully with proposed specifications for the product in its market package. Stability data from at least three lots are usually required for licensure approval.

2. Supportive Data

The approved expiration dating period of a biological product is normally based upon the interval of time for which data are available under the storage conditions stated in the labeling. Studies that address the stability of the product when in bulk storage (prior to filling) may be

considered to support the expiration dating period of the finished drug product. In addition, the effects of temperature extremes that may be encountered during shipment of the product should be determined.

3. Expiration Dating Period Granted with Commitment

In some instances, the stability data may not cover the full period desired. It is possible to grant the desired expiration dating period provided that all data and information clearly support this conclusion and there is a sufficient lead time for development of data covering the desired expiration dating period. The standard commitment to continue the stability study at the recommended storage condition, also must be submitted for confirmation.

C. Amendments

1. Change in Formulation and Container-Closure

An amendment to an approved PLA that proposes a change in the product's formulation, including, the culture media for growing live organisms or in the container-closure for the marketed product, will usually require the development of data to show that the proposed change has not adversely affected the product's stability . In certain instances, accelerated storage data demonstrating comparability with the previously approved product plus the standard

commitment will suffice. For certain biological products that are known to be relatively unstable, this may require a minimum of 6 months' data at the normal recommended storage temperature together with data from accelerated conditions.

2. New Manufacturing Facility

For a proposed change to a new manufacturing facility for the same licensed product using similar equipment, accelerated data should be submitted, if feasible. A commitment to conduct stability studies on a minimum of the first three lots produced in the new facility should also be submitted. Ordinarily, the previously approved expiration dating period may be used under these circumstances.

3. Extension of Expiration Dating Period

An amendment requesting an extension in the expiration dating period should be accompanied by supporting updated stability data.

4. Reprocessed Material

When appropriate, an amendment providing for the use of reprocessed material should include data to ensure that the reprocessed product will meet final product specifications.

The standard commitment to subject any lots of the product made from reprocessed material to stability testing should accompany the amendment.

VII. CONTENT OF STABILITY REPORTS

It is suggested that stability reports include the following information and data to facilitate decisions concerning the stability proposals:

A. General Product Information

1. Name of drug substance and drug product or biological product.

2. Dosage form and strength, including formulation. (The application should provide a table of specific formulations under study when more than one formulation has been studied.)

3. Labeling.

4. Composition, type, and size of container-closure.

B. Specifications and Test Methodology Information

1. Physical, chemical, and microbiological characteristics and prior submission specifications (or specific references to NDA or USP).

2. Test methodology used (or specific reference to NDA, prior submissions, or USP) for each sample tested.

3. Information on accuracy, precision, and suitability of the methodology (cited by reference to appropriate sections).

4. For biological products, a description of the potency test(s) for measuring biological activity, including specifications for potency determination.

C. Study Design and Study Conditions

1. Description of the sampling plan, including:

   a. Batches and number selected.

   b. Container-closures and number selected.

   c. Number of dosage units selected and whether tests were conducted on individual units or on composites of individual units.

   d. Sampling times.

   e. Testing of drug or biological products for reconstitution at the time of dispensing (as directed on the labeling) as well as after they are reconstituted.

2. Expected duration of the study.

3. Conditions of storage of the product under study (temperature, humidity, light).

D. Stability Data/Information

1. Lot number (research, pilot, production) and associated manufacturing date.

2. For antibiotic drug products, the age of the bulk active drug substance(s) used in manufacturing the lot.

3. Analytical data and source of each data point (e.g., lot, container, composite, etc). Pooled estimates may be submitted if individual data points are provided.

4. Summary of information on previous formulations obtained during product development maybe (referenced if previously submitted). Summary should include other container-closures investigated.

E. Data Analysis and Conclusions

1. Documentation of appropriate statistical methods and formulas used in the analysis.

2. Evaluation of data, including calculations, statistical analysis, plots, or graphics.

3. Results of statistical tests used in arriving at microbiological potency estimates.

4. Proposed expiration dating period and its justification.

5. Release specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted).

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