Guidance for Industry

Stability Testing of Drug Substances and Drug Products

DRAFT GUIDANCE

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Copies of this draft guidance are available from the Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857 (Phone 301-827-4573) or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at http://www.fda.gov/cber/guidelines.htm. Copies also may be obtained by fax from 1-888-CBERFAX or 301-827-3844 or by mail from the Voice Information System at 800-835-4709 or 301-827-1800.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Stability Testing of Drug Substances and Drug Products

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please identify specific comments by line number.)

I. INTRODUCTION

The guidance is intended to be a comprehensive document that provides information on all aspects of stability data generation and use. It references and incorporates substantial text from the following International Conference on Harmonization (ICH) guidance:

- *ICH Harmonized Tripartite Guideline for Stability Testing of New Drug Substances and Products, September 23, 1994* [ICH Q1A]
- *ICH Guideline for Stability Testing of New Dosage Forms* [ICH Q1C]
- *ICH Guideline for Photostability Testing of New Drug Substances and Products* [ICH Q1B]
- *ICH Guideline for Stability Testing of Biotechnological/Biological Products* [ICH Q5C].

Where text from one of these documents has been incorporated in this guidance, it has been denoted by the use of a reference in square brackets in the beginning of a particular section or at the end of an individual paragraph.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf lives. [ICH Q1A]

This guidance provides recommendations regarding the design, conduct and use of stability studies that should be performed to support:

- Investigational new drug applications (INDs) (21 CFR 312.23(a)(7)),

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[1] This guidance has been prepared by the Stability Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee (CMCCC) of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration with input from the Center for Biologics Evaluation and Research (CBER). This guidance document represents the Agency's current thinking on stability testing of drug substances and products. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both.

- New drug applications (NDAs) for both new molecular entities (NMEs) and non-NMEs,
- New dosage forms (21 CFR 314.50(d)(1)),
- Abbreviated new drug applications (ANDAs) (21 CFR 314.92 - 314.99),
- Supplements and annual reports (21 CFR 314.70, and 601.12),
- Biologics license application (BLAs) and product license applications (PLAs) (21 CFR 601.2).

The principle established in ICH Q1A — that information on stability generated in any one of the three areas of the EU, Japan, and the USA would be mutually acceptable in both of the other two areas — is incorporated in this guidance document. In fact, much of the text of the guidance on drug substances and drug products (Sections II.A. and II.B.) is incorporated directly from the ICH Q1A text.

This guidance is intended to replace the *Guideline For Submitting Documentation for the Stability of Human Drugs and Biologics*, published in February 1987. It applies to all drug substances and products submitted to the Center for Drug Evaluation and Research (CDER). This guidance also applies to biological products that are included in the scope of the ICH Q5C Stability Annex, *Stability Testing of Biotechnology Drug Products* (July 1996) and all other products submitted to the Center for Biologics Evaluation and Research (CBER).

The guidance provides recommendations for the design of stability studies for drug substances and drug products that should result in a statistically acceptable level of confidence for the established retest or expiration dating period for each type of application. The applicant is responsible for confirming the originally established retest and expiration dating periods by continual assessment of stability properties (21 CFR 211.166). Continuing confirmation of these dating periods should be an important consideration in the applicant's stability program.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the EU, Japan, and the USA. The mean kinetic temperature in any region of the world can be derived from climatic data (Grimm, W., Drugs Made in Germany, 28:196-202, 1985, and 29:39-47, 1986). [ICH Q1A]

The recommendations in this guidance are effective upon publication of the final guidance and should be followed in preparing new applications, resubmissions, and supplements. This guidance represents FDA's current thinking on how the stability section of drug and biologics applications should be prepared. An applicant may choose to use alternative procedures. If an applicant chooses to depart from the recommendations set forth in this guidance, the applicant is encouraged to discuss the matter with FDA prior to initiating studies that may later be determined to be unacceptable.

FDA recognizes that the time necessary for applicants to establish new procedures, install, and commission the new temperature and relative humidity-controlled rooms/cabinets, carry out appropriate stability studies on batches of product, and submit the information in an application may prevent some applicants from generating data consistent with the recommendations in the guidance for some time. However, since this guidance represents FDA's current thinking and recommendations regarding stability, submission of data not conforming with this guidance is possible with justification. Applications withdrawn prior to publication of this guidance should not normally have to include stability data in conformance with the guidance upon resubmission. However, if new stability studies are conducted to support the submission, such studies should be conducted as recommended in the guidance.

A comprehensive glossary has been included, which contains definitions of the major terms and the origin of the definitions (e.g., ICH, CFR, USP) where applicable.

II. STABILITY TESTING FOR NEW DRUG APPLICATIONS

A. Drug Substance

Information on the stability of a drug substance under defined storage conditions is an integral part of the systematic approach to stability evaluation. Stress testing helps to determine the intrinsic stability characteristics of a molecule by establishing degradation pathways to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the drug substance. These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance and type of drug product.

This testing is likely to be carried out on a single batch of a drug substance. Testing should include the effects of temperatures in 10°C increments above the accelerated temperature test condition (e.g., 50°C, 60°C) and humidity, where appropriate (e.g., 75 percent or greater). In addition, oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension should be evaluated. Results from these studies will form an integral part of the information provided to regulatory authorities. Light testing should be an integral part of stress testing. The standard test conditions for photostability are discussed in the ICH Q1B guidance.

It is recognized that some degradation pathways can be complex and that under forced conditions, decomposition products may be observed that are unlikely to be formed under accelerated or long-term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products if it has been demonstrated that in practice these are not formed.

Primary stability studies are intended to show that a drug substance will remain within specifications during the retest period if stored under recommended storage conditions. [ICH Q1A].

1. Selection of Batches

Stability information from accelerated and long-term testing should be provided on at least three batches. Long-term testing should cover a minimum of 12 months' duration on at least three batches at the time of submission. The batches manufactured to a minimum of pilot plant scale should be by the same synthetic route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale. The overall quality of the batches of drug substance placed on stability should be representative of both the quality of the material used in preclinical and clinical studies and the quality of material to be made on a manufacturing scale. Supporting information may be provided using stability data on batches of drug substance made on a laboratory scale. [ICH Q1A]

The first three production batches[2] of drug substance manufactured post approval, if not submitted in the original drug application, should be placed on long-term stability studies post approval, using the same stability protocol as in the approved drug application. [ICH Q1A]

2. Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical, biological, and microbiological test characteristics. Validated stability-indicating test methods should be applied. The extent of replication will depend on the results of validation studies. [ICH Q1A]

3. Specifications

Limits of acceptability should be derived from the quality profile of the material as used in the preclinical and clinical batches. Specifications will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials. [ICH Q1A]

4. Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature-sensitive drug substances should be stored under an alternative lower temperature condition, which will then become the designated long-term testing storage temperature. The 6-month accelerated testing should then be carried out at a temperature at least 15°C above this designated long-term storage temperature (together with the appropriate

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[2] The terms *production batch* and *manufacturing scale production batch* are used interchangeably throughout this guidance to mean a batch of drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

relative humidity conditions for that temperature). The designated long-term testing conditions will be reflected in the labeling and retest date. [ICH Q1A]

Where *significant change* occurs during 6 months of storage under conditions of accelerated testing at 40°C ± 2°C/75% RH± 5%, additional testing at an intermediate condition (such as 30°C± 2°C/60% RH± 5%) should be conducted for a drug substance to be used in the manufacture of a dosage form tested for long-term at 25°C ± 2°C/60% RH ± 5% and this information should be included in the drug application.[3] The initial drug application should include at the intermediate storage condition a minimum of 6 months of data from a 12-month study. [ICH Q1A]

Significant change at 40°C/75% RH or 30°C/60% RH is defined as failure to meet the specifications.[ICH Q1A] If any parameter fails *significant change* criteria during the accelerated stability study, testing of all parameters during the intermediate stability study should be performed.

If stability samples have been put into the intermediate condition, but have not been tested, these samples may be tested as soon as the accelerated study shows significant change in the drug substance. Alternatively, the study at the intermediate condition would be started from the initial time point.

Where a *significant change* occurs during 12 months of storage at 30ºC/60%RH, it may not be appropriate to label the drug substance for controlled room temperature (CRT) storage with the proposed retest period even if the stability data from the full long-term studies at 25ºC/60%RH appear satisfactory. In such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant, shorter retest period, refrigerator temperature storage, or more protective container and/or closure, should be considered during drug development.

The long-term testing should be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods, and the further accumulated data can be submitted to the FDA during the assessment period of the drug application. [ICH Q1A]

The data (from accelerated testing and/or from testing at an intermediate storage condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. [ICH Q1A]

5. Testing Frequency

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[3] The equipment must be capable of controlling temperature to a range of ± 2°C and relative humidity to ± 5% RH. The actual temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed by the applicant and reported if judged to impact stability results. Excursions that exceed these ranges (i.e., ± 2°C and/or ± 5% RH) for more than 24 hours should be described and their impact assessed in the study report.

Frequency of testing should be sufficient to establish the stability characteristics of the drug substance. Testing under the defined long-term conditions will normally be every 3 months over the first year, every 6 months over the second year, and then annually. [ICH Q1A]

6. Packaging /Containers

The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution. [ICH Q1A]

7. Evaluation

The design of the stability study is to establish a retest period applicable to all future batches of the bulk drug substance manufactured under similar circumstances, based on testing a minimum of three batches of the drug substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics). The degree of variability of individual batches affects the confidence that a future production batch will remain within specifications until the retest date. [ICH Q1A]

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95 percent one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits. [ICH Q1A]

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve. [ICH Q1A]

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a full justification for the omission is usually sufficient. [ICH Q1A]

Limited extrapolation may be undertaken of the real-time data beyond the observed range to extend retest period at approval time, particularly where the accelerated data support this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about such factors as the mechanism of degradation, the goodness of fit of any mathematical model, batch size, and existence of supportive data. Any evaluation should cover not only the assay, but the levels of degradation products and other appropriate attributes. [ICH Q1A]

8. Statements/Labeling

A storage temperature range may be used in accordance with relevant national/regional requirements. The range should be based on the stability evaluation of the drug substance. Where applicable, specific requirements should be stated, particularly for drug substances that cannot tolerate freezing. The use of terms such as *ambient conditions* or *room temperature* is unacceptable. [ICH Q1A]

A retest period should be derived from the stability information. [ICH Q1A]

B. Drug Product

1. General

The design of the stability protocol for the drug product should be based on the knowledge obtained on the behavior, properties, and stability of the drug substance and the experience gained from clinical formulation studies. The changes likely to occur upon storage and the rationale for the selection of drug product parameters to be monitored should be stated. [ICH Q1A]

2. Selection of Batches

Stability information from accelerated and long-term testing is to be provided on three batches of the same formulation of the dosage form in the container and closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g., 25,000 to 50,000 tablets or capsules for solid oral dosage forms). The long-term testing should cover at least 12 months' duration at the time of submission. The manufacturing process to be used should meaningfully simulate that to be applied to large-scale production batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification to be applied for release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of the drug substance. [ICH Q1A]

Data on laboratory-scale batches are not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information. The first three production batches manufactured post approval, if not submitted in the original application, should be placed on accelerated and long-term stability studies using the same stability protocols as in the approved drug application. [ICH Q1A]

3. Test Procedures and Test Criteria

The test parameters should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated and the assays should be stability-indicating. The need for replication will depend on the results of validation studies. [ICH Q1A]

The range of testing should cover not only chemical and biological stability, but also loss of preservative, physical properties and characteristics, organoleptic properties, and where required, microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives. [ICH Q1A]

4. Specifications

Where applicable, limits of acceptance should relate to the release limits to be derived from consideration of all the available stability information. The shelf-life specifications could allow acceptable and justifiable deviations from the release specifications based on the stability evaluation and the changes observed on storage. They need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials. The justification for the limits proposed for certain other tests, such as particle size and/or dissolution rate, will require reference to the results observed for the batch(es) used in bioavailability and/or clinical studies. Any differences between the release and shelf-life specifications for antimicrobial preservatives content should be supported by preservative efficacy testing. [ICH Q1A]

5. Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use (e.g., reconstitution or dilution as recommended in the labeling). See Table 1 below for recommended accelerated and long-term storage conditions and minimum times. Assurance that long-term testing will continue to cover the expected shelf life should be provided. [ICH Q1A]

Other storage conditions are allowable if justified. Heat-sensitive drug products should be stored under an alternative lower temperature condition, which will eventually become the designated long-term storage temperature. Special consideration may need to be given to products that change physically or even chemically at lower storage temperatures (e.g., suspensions or emulsions which may sediment, or cream, oils and semi-solid preparations, which may show an increased viscosity). Where a lower temperature condition is used, the 6-month accelerated testing should be carried out at a temperature at least 15°C above its designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long-term under refrigerated conditions, accelerated testing should be conducted at 25°C ± 2°C/60% RH ± 5%. The designated long-term testing conditions will be reflected in the labeling and expiration date. [ICH Q1A]

Storage under conditions of high relative humidity applies particularly to solid dosage forms. For drug products such as solutions and suspensions contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary but the same range of temperatures should be applied. Low relative humidity (e.g., 10 - 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers), and consideration should be given to appropriate testing under such conditions. [ICH Q1A]

Table 1: Long-Term/Accelerated Testing Conditions

	Conditions	Minimum time period at submission
Long-term testing	25°C ± 2°C/60% RH ± 5%	12 Months
Accelerated Testing	40°C ± 2°C/75% RH ± 5%	6 Months

Where *significant change* occurs due to accelerated testing, additional testing at an intermediate condition (e.g., 30°C± 2°C/60% RH ± 5%) should be conducted. *Significant change* at the accelerated conditions is defined as:

1. A 5 percent potency loss from the initial assay value of a batch.
2. Any specified degradant exceeding its specification limit.
3. The product exceeding its pH limits.
4. Dissolution exceeding the specification limits for 12 capsules or tablets (USP Stage 2).
5. Failure to meet specifications for appearance and physical properties (e.g., color, phase separation, resuspendability, delivery per actuation, caking, hardness) [ICH Q1A].

Should significant change occur at 40°C/75% RH, the initial application should include a minimum of 6 months' data from an ongoing 1-year study at 30°C/60 percent RH; the same significant change criteria shall then apply. [ICH Q1A]

If any parameter fails *significant change* criteria during the accelerated stability study, testing of all parameters during the intermediate stability study should be performed.

If stability samples have been put into the intermediate condition, but have not been tested, testing these samples may begin as soon as the accelerated study shows significant change in the drug product. Alternatively, the study at the intermediate condition would be started from the initial time point.

Where a *significant change* occurs during 12 months of storage at 30ºC/60%RH, it may not be appropriate to label the drug product for CRT storage with the proposed expiration dating period even if the stability data from the full long-term studies at 25ºC/60%RH appear satisfactory. In such cases, alternate approaches, such as qualifying higher acceptance criteria for a degradant, shorter expiration dating period, refrigerator temperature storage, more protective container and/or closure, modification to the formulation and/or manufacturing process, should be considered during drug development. If CRT storage is ultimately justified, it may be necessary to add to the product labeling a cautionary statement against prolonged exposure at or above 30ºC.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover shelf life at appropriate test periods. The further accumulated data should be submitted to the FDA during the assessment period of the drug application. [ICH Q1A]

The first three production batches manufactured post approval, if not submitted in the original application, should be placed on accelerated and long-term stability studies using the same stability protocol as in the approved drug application. [ICH Q1A] A minimum of 4 test stations (e.g., 0, 2, 4, and 6 months) are recommended for the 6-month accelerated stability study.

6. Stability Storage Conditions not Defined in ICH Q1A

The stability sample storage conditions for most dosage forms (e.g., solid oral dosage forms, solids for reconstitution, dry and lyophilized powders in glass vials) are defined in Section V.E. of the ICH Q1A Guidance and in Section II.B.5 of this guidance. However, the stability storage conditions are not indicated in ICH Q1A for certain other drug products including those packaged in semi-permeable containers (except for accelerated studies), products intended to be stored under refrigerator or freezer temperatures, or certain studies on metered dose inhalations (MDIs) and dry powder inhalers (DPIs). Further information about these products and containers is provided in this section.

a. Stability Storage Conditions for Drug Products in Semi-Permeable and Permeable Containers

For large volume parenterals (LVPs), small volume parenterals (SVPs), ophthalmics, otics, and nasal sprays packaged in semi-permeable containers, such as plastic bags, semi-rigid plastic containers, ampules, vials and bottles with or without droppers/applicators, which may be susceptible to water loss, the recommended stability storage conditions are:

- Accelerated condition: 40°C ± 2°C/15% RH ± 5% (hereafter referred to as 40°C/15% RH)[ICH Q1A];
- Intermediate condition: 30°C ± 2°C/40% RH ± 5% (hereafter referred to as 30°C/40% RH);
- Long-term condition: 25°C ± 2°C/40% RH ± 5%

For liquids in glass bottles, vials, or sealed glass ampules, which provide an impermeable barrier to water loss,

- Accelerated condition: 40°C/ambient humidity is an acceptable alternative to 40°C/75% RH;
- Intermediate condition: 30°C/ambient humidity is an acceptable alternative to 30°C/60% RH;
- Long-term condition: 25°C/ambient humidity is an acceptable alternative to 25°C/60% RH.

b. Stability Storage Conditions for Drug Products Intended to be Stored at Refrigerator Temperature

- Accelerated conditions: 25°C/60% RH, with ambient humidity an acceptable alternative for aqueous products that would not be affected by humidity conditions;
- Long-term conditions: 5°C ± 3°C, with monitoring, but not control of, humidity.

c. Stability Storage Conditions for Drug Products Intended to be Stored at Freezer Temperature

- Accelerated conditions: 5°C ± 3°C/ambient humidity;
- Long-term conditions: -15°C ± 5°C.

d. Stability Storage Conditions for Some Inhalation Products

Additional storage conditions may apply to inhalation powders and suspension inhalation aerosols when significant change in aerodynamic particle size distribution or in dose content uniformity occurs at accelerated conditions (40C/75%RH). (The Agency currently is developing a draft guidance to address chemistry, manufacturing, and controls documentation for MDIs and DPIs.)

7. Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug product. Testing will normally be every 3 months over the first year, every 6 months over the second year, and then annually. Matrixing or bracketing can be used, if justified. [ICH Q1A] A minimum of 4 test stations (e.g., 0, 2, 4, and 6 months) are recommended for the 6-month accelerated stability study.

8. Application of ICH Stability Study Storage Conditions to Approved Applications

Although the ICH Guidance for *Stability Testing of New Drug Substances and Products* applies only to new molecular entities and associated drug products, applicants may wish to voluntarily switch to the ICH-recommended storage conditions as defined in ICH Q1A and Sections II.A.4. and II.B.5. of this guidance or other FDA-recommended conditions as described in Section II.B.6. of this guidance, as appropriate, for previously approved drug or biologic products. Applicants are not required to make such a switch for either annual stability batches or batches intended to support supplemental changes. Although the following discussions refer only to the ICH conditions, the same recommendations can be applied when a switch to other FDA-recommended conditions is contemplated.

Two plans are presented to assist applicants who desire to switch their approved drug products to the ICH-recommended storage conditions. Under each plan, recommendations will be made on how to initiate a switch to the ICH storage testing conditions, select batches, collect data, report results, and proceed if products fail the approved specifications under the ICH conditions.

a. Plan A: Using the ICH Storage Testing Conditions for an Approved Stability Protocol

This plan may be most suitable for drug products that have been confirmed to be stable when exposed to the controlled level of humidity on a long-term basis. Only one set of conditions (i.e., the ICH conditions) and one set of testing for each of the three verification batches, as defined below, are necessary under this plan.

i. Drug Products with an Approved Stability Protocol

Applicants who have previously performed drug product stability studies under an approved protocol at 25°C, 30°C, or 25-30°C without humidity controls may switch over to the ICH long-term conditions, as defined in V.E. of the ICH Q1A guidance and incorporated in Section II.B. of this guidance, for all of their annual stability studies. A revised stability protocol may be submitted in the annual report, reflecting changes in temperature and humidity to conform with those recommended by the ICH. Any other changes to the stability protocol should be submitted as a prior-approval supplement. Once adopted through an annual report, the ICH conditions should be used to generate stability data for subsequent supplemental changes. Alternatively, the applicant may report the ICH switch in a supplement, which requires stability data, if the supplement occurs before the next scheduled annual report. Data from the first three consecutive annual batches after the switch can be used to verify the previously approved expiration dating period. However, if the applicant wishes to verify product stability under the ICH conditions over a shorter time span, three production batches within one year, instead of three consecutive annual batches, may be studied.

ii. Products Without an Approved Stability Protocol

Applicants who have previously performed stability studies on a drug product without an approved protocol are required to submit an appropriate protocol under a prior-approval supplement under 21 CFR 314.70(b) or (g) or 601.12(b) (see Section V regarding an Approved Stability Protocol). Upon approval of the protocol, applicants may initiate stability studies on all annual batches under the ICH long-term conditions. Data from the first three consecutive annual batches after the switch can be used to verify the current, or to establish a new, expiration dating period. However, if the applicant wishes to verify product stability under the ICH conditions over a shorter time span, three production batches within one year, instead of three consecutive annual batches, may be studied

iii. Stability Data for Supplemental Changes

Stability data submitted in support of supplemental changes for an existing drug product may be generated with samples stored at the ICH-recommended accelerated testing conditions, and long-term testing conditions, and, if applicable, intermediate conditions, as described in V.E. of the ICH Q1A guidance (Section II.B. of this guidance) or Section III.B of this guidance.

iv. Other Considerations

For a moisture-sensitive product, the applicant may wish to explore the possibility of improving the container/closure before embarking on the switch-over to the ICH condition.

Although 30°C/60% RH is an acceptable alternative to 25°C/60% RH for long-term studies, these conditions should not be used as the basis for a labeling statement such as “Store at 30°C” or “Store at 15-30°C” to gain marketing advantage.

With respect to ongoing stability studies, applicants may carry them to completion under the previously approved conditions or may, for practical or economic reasons, choose to make an immediate switch to ICH conditions and report the change in the next annual report.

v. Data Submission to FDA

Satisfactory data:

> If the stability data generated on the first three annual batches after the switch to the ICH-recommended long-term testing conditions using an approved protocol, as defined above, support the previously approved expiration dating period under the non-ICH conditions, the data can be submitted in the next annual report, and the current expiration dating period can be retained.

Unsatisfactory data:

> If the stability data under the ICH conditions fall outside the specifications established for the previously approved expiration dating period, the applicant should perform an investigation to determine the probable cause of the failure in accordance with CGMP regulations under 21 CFR 211.192. Additionally, the applicant should submit an NDA Field-Alert Report in accordance with 21 CFR 314.81(b)(1)(ii) or an error and accident report for a biological product under 21 CFR 600.14. A recall of the corresponding product in the market place may also be necessary. If it is determined that the ICH storage conditions, particularly the added humidity, is the cause for the stability failure, the applicant may shorten the expiration dating period in a changes-being-effected supplement while retaining the ICH storage condition. Subsequently, if justified, the applicant may request an approval for a revision of the product specifications and for reinstating the previously approved expiration dating period under the non-ICH conditions through a prior-approval supplement. Other measures (e.g., more protective container/closure or product reformulation) may be considered through a prior-approval supplement.
>
> Alternatively, the applicant may, after careful consideration of all aspects, request for a return to the previous storage conditions in a changes-being-effected supplement if justification, including all related data and investigational results, is provided.

b. Plan B: Using the ICH Conditions under an Alternate Protocol

An alternative to Plan A is to conduct two side-by-side studies by simultaneously placing samples from the same batch of drug product under the ICH conditions as well as the previously approved storage condition. The protocol containing the ICH storage conditions is considered an alternative to the approved protocol. This plan may prove to be particularly useful if the drug product is believed to be moisture-sensitive.

i. Products with an Approved Stability Protocol

Applicants may initiate stability studies under the ICH-recommended long-term testing conditions, in addition to the previously approved conditions at 25°C, 30°C, or 25-30°C without humidity controls, for three consecutive annual batches. Data from these annual batches under the ICH conditions should be used to verify the current expiration dating period. However, if the applicant wishes to verify the ICH conditions over a shorter time span, three production batches within one year or less may be selected, instead of three consecutive annual batches.

ii. Products without an Approved Stability Protocol

Applicants who have previously performed stability studies on a drug product without an approved protocol should submit an appropriate protocol as a prior-approval supplement. This protocol should contain 25°C/ambient humidity as the primary long-term storage testing conditions and the ICH long-term conditions, as the alternative, as well as the IC-recommended accelerated testing conditions. Upon approval of the protocol, applicants may initiate stability studies on three consecutive annual batches at both 25°C/ambient humidity and 25°C/60% RH or 25°C/40% RH. Data from these annual batches under the ICH conditions can be used to verify the current, or to establish a new, expiration dating period.

iii. Other Considerations

Same as in Plan A.

iv. Protocol Revisions

Products with an approved stability protocol:

> Applicants who have an approved stability protocol may submit the alternate stability protocol in the annual report, reflecting the temperature and humidity as recommended by the ICH. Other changes to the stability protocol generally should be submitted in a prior-approval supplement, unless the changes are to comply with the current compendium.
>
> Once adopted as an alternate protocol through an annual report, the ICH conditions can be used, in parallel with the previously approved conditions, to generate stability data for subsequent supplemental changes. Alternatively, the applicant may report the alternative ICH conditions in a supplement, which requires stability data, if the supplement occurs before the next scheduled annual report.
>
> If the complete stability data generated on the first three annual batches under the ICH long-term conditions using an approved alternate protocol (as defined above) support the previously approved expiration dating period under the non-ICH conditions, the alternate stability protocol can be adopted as the primary stability protocol through an annual report.

Products without an approved stability protocol:

> For applications that do not contain an approved stability protocol as defined above, a new or revised stability protocol may be submitted in a prior-approval supplement marked *expedited review requested*. This protocol should encompass 25°C/ambient humidity as the primary long-term storage conditions and the ICH long-term conditions, as the alternate, as well as

accelerated stability storage conditions, as defined by the ICH Guidance and above, and other recommendations described in this guidance. Upon approval of the protocol, stability studies may be initiated on annual batches and batches intended to support supplemental changes.

v. Stability Data for Supplemental Changes

Applicants may provide stability data in support of postapproval supplemental changes with samples stored at the ICH-recommended accelerated testing conditions and long-term testing conditions, both previously approved and ICH, as well as, if applicable, intermediate conditions. See Change in Stability Protocol (Section IX.J.) for the recommended filing mechanism.

vi. Data Submission

Satisfactory data:

If the complete stability data generated on the first three annual batches under the ICH long-term conditions using an approved alternate protocol support the previously approved expiration dating period under the non-ICH conditions, the data can be submitted in the annual report and the current expiration dating period can be retained.

Unsatisfactory data

If the stability data under the ICH conditions fall outside the acceptance criteria while data from the parallel study under the previously approved conditions or 25°C/ambient humidity, whichever applies, are satisfactory during the previously approved expiration dating period, and the added humidity is determined to be the cause for the stability failure, the product will still be considered to be in compliance with the regulatory specifications approved in the application. If the applicant decides to adopt the ICH conditions, a changes-being-effected supplement with shortened expiration dating period or a prior-approval supplement with revised product specifications may be submitted where justified. Other measures (e.g., more protective container/closure or product reformulation) may be considered through a prior-approval supplement.

Alternatively, after careful consideration of all aspects, the applicant may decide not to pursue the switch-over to the ICH conditions for the product. The applicant may eliminate the alternate stability protocol in the next annual report if a full explanation, including all related data and investigational results, is provided.

In the case where the product fails to meet the specifications under the non-ICH conditions, irrespective of whether it also fails under the ICH conditions, a thorough investigation in accordance with CGMP should be performed and appropriate corrective actions should be taken, including a Field-Alert Report and recall of the affected product from the market place if warranted.

9. Packaging Materials [ICH Q1A]

The testing should be carried out in the final packaging proposed for marketing. Additional testing of the unprotected drug product can form a useful part of the stress testing and package evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

10. Evaluation [ICH Q1A]

A systematic approach should be adopted in the presentation of the evaluation of the stability information, which should cover, as necessary, physical, chemical, biological and microbiological quality characteristics, including particular properties of the dosage form (for example, dissolution rate for oral solid dose forms).

The design of the stability study is to establish a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances based on testing a minimum of three batches of the drug product. The degree of variability of individual batches affects the confidence that a future production batch will remain within specifications until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95 percent one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it may be advantageous to combine the data into one overall estimate by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If combining data from several batches is inappropriate, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function of an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; but a justification for the omission should be provided.

Limited extrapolation may be taken of the real-time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data support this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about such factors as the mechanism of degradation, the goodness of fit of any mathematical model, batch size, and existence of supportive data.

Any evaluation should cover not only the assay, but also the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability, and degradation performance.

The stability of the drug product after reconstituting or diluting according to labeling should be addressed to provide appropriate and supportive information.

See Section VIII.N. for additional information on drug products which are reconstituted or diluted.

11. Statements/Labeling

A storage temperature range may be used in accordance with FDA regulations. The range should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated, particularly for drug products that cannot tolerate freezing.

The use of terms such as *ambient conditions* or *room temperature* is unacceptable.

There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product.

A single set of uniform storage statements (USSs) for NDAs, ANDAs, PLAs and BLAs is recommended to avoid different labeling storage statements for products stored under controlled room temperature conditions. The storage statements and storage conditions provided in this section of the guidance are intended to be standardized and harmonized with the CRT definition in the USP and the recommendations in the ICH guidance.

a. Room Temperature Storage Statements

i. Liquid Dosage Forms in Semi-Permeable Containers

The recommended storage statement for LVPs, SVPs, ophthalmics, otics and nasal sprays packaged in semi-permeable containers, such as plastic bags, semi-rigid plastic containers, ampules, vials and bottles with or without droppers/applicators, that may be susceptible to water loss but have been demonstrated to be stable at 25°C ± 2°C/40% or 60% RH ± 5% (or 30°C ± 2°C/40% or 60% RH ± 5%); at 25°C/NMT 40% or 30°C/NMT 40% RH; or 30°C, 25-30°C, or 25°C without humidity controls, is:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

For sterile water for injection (WFI) and LVP solutions of inorganic salts packaged in semi-permeable containers (e.g., plastic bags) the following statement may be used on the immediate container labels:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]
(see insert for further information)

and the following statement may be used in the "How Supplied" section of the package insert:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]
Brief exposure to temperatures up to 40°C/104°F may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F).
However, such exposure should be minimized.

LVP solutions packaged in a semi-permeable container (e.g., a plastic bag) and containing simple organic salts (e.g.,acetate, citrate, gluconate, and lactate, and dextrose 10 percent or less) may be labeled as above, provided there are adequate stability data (at least 3 months' at 40°C ± 2°C/15% RH± 5% or 40°C/NMT 20% RH) to support such labeling.

ii. All Other Dosage Forms

For all other dosage forms (e.g., solid oral dosage forms, dry powders, aqueous liquid, semi-solid and suspension dosage forms) that have been demonstrated to be stable at the ICH-recommended conditions (25°C ± 2°C/60% RH ± 5%, or 30°C/60% RH ± 5%) or at non-ICH conditions, such as 30°C, 25-30°C, or 25°C without humidity controls and intended to be stored at room temperature, the recommended labeling statement is:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature]

iii. Where Space on the Immediate Container is Limited

Where an abbreviated labeling statement is necessary because space on the immediate container is limited, either of the following statements is acceptable provided the full labeling statement, as shown above, appears on the outer carton and in the package insert:

Store at 25°C (77°F); excursions 15-30°C (59-86°F)
Store at 25°C (77°F) (see insert)

b. Refrigerator Storage Statement

For a drug product demonstrated to be stable at 5°C ± 3°C, 2-5°C, or 2-8°C with or without humidity control and which is intended to be stored at refrigerator temperature, the recommended storage statement for labeling may be one of the following:

Store in a refrigerator, 2-8°C (36-46°F)
Store refrigerated, 2-8°C (36-46°F)

Where an abbreviated labeling statement is necessary because space on the immediate container is limited, the following statement is acceptable, provided one of the full labeling statements, as shown above, appears on the outer container and in the package insert:

Refrigerate (see insert)

c. Room Temperature and/or Refrigerator Storage Statement

For a drug product demonstrated to be stable both at 25°C ± 2°C/60% RH ± 5% and at refrigerator temperature, either/or both of the room temperature and refrigerator labeling statements, as described above, are acceptable, depending on the storage conditions intended for the product. A statement such as “store at 2-25°C” is not recommended.

d. Additional Cautionary Statements

If warranted, additional cautionary statements to protect a drug product from excessive heat, light, humidity, freezing, and other damaging conditions, should be included on the container label and the package insert. If the space on the container label is too limited to display all the recommended statements in detail, a reference to the package insert for further information (e.g., *see insert*) is recommended. The uniform storage statements and stability conditions are summarized in Tables 2 and 3, respectively.

Table 2: Summary of Uniform Storage Statements in Drug Product Labeling

		Recommended Storage Statement in Drug Product Labeling	
		Full	Abbreviated
Intended storage conditions for drug product	Room Temperature	Store at 25°C (77/F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]	Store at 25/C (77°F) excursions 15-30°C (59-86°F) or Store at 25°C (77°F) (see insert)
	Refrigerator Temperature	Store in a refrigerator, 2-8°C (36-46°F) or Store refrigerated	Refrigerate (see insert)

Table 3: Conditions under which Product has been Shown to be Stable to Apply Uniform Storage Statements

Intended storage conditions for drug product	Room Temperature		Refrigerator Temperature
Type of product	LVP in a plastic bag[a] or Aqueous Solution in a LDPE bottle or prefilled syringe	All other types	All drug products (as appropriate)
Conditions under which product has been shown to be stable	25°C ± 2°C/60% RH ±5% 30°C ± 2°C/40% RH ± 5% 25°C/NMT 40% RH 30°C/NMT 40% RH or 25°C, 30°C or 25-30°C and ambient humidity	25°C ± 2°C /60% RH ± 5% 30°C/60% RH ± 5% or 25°C, 30°C or 25-30°C and ambient humidity	5°C ± 3°C 2-5°C or 2-8°C

[a] See Section II.B.11.a. for additional information on sterile water for injection and LVPs containing inorganic salts or simple organic salts.

e. Other Considerations

The applicant may wish to include the definition of USP CRT in its entirety in the package insert to provide easy reference.

f. Implementation of the USSs in Labeling for New Product Applications

The recommended storage statements in labeling should be adopted for new or pending NDA, ANDA, BLA or PLA products. For applications approved prior to the publication of the guidance, the recommended storage statements should be adopted through the annual report mechanism at the next printing opportunity if desired, but within three years of the date of the final guidance. With respect to room temperature storage statements for already approved products, new stability studies under the ICH conditions are not required to adopt the recommended room temperature labeling statements, provided the products have been demonstrated to be stable through expiry under one of the following controlled temperatures: 30°C, 25-30°C, 25°C and at ambient humidity.

C. New Dosage Forms [ICH Q1C]

A new dosage form is defined as a drug product that is a different pharmaceutical product type, but contains the same active substance as included in an existing drug product approved by the FDA.

New dosage forms include products of different administration route (e.g., oral, when the original new drug product was a parenteral), new specific functionality/delivery system (e.g., modified release tablet, when the original new drug product was an immediate release tablet, and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms should follow the guidance in the ICH Q1A in principle. However, a reduced stability database at submission time (e.g., 6 months' accelerated and 6 months' long-term data from ongoing studies) may be acceptable in certain justified cases.

D. Other NDAs

Stability protocols for new combination products or new formulations (which require clinical data for approval) should follow the guidance in the ICH Q1A in principle. However, a reduced stability database at submission time (e.g., 6 months' accelerated and 6 months' data from ongoing studies at the long-term condition) may be acceptable in certain justified cases, such as when there is a significant body of information on the stability of the drug product and the dosage form.

III. STABILITY TESTING FOR ABBREVIATED NEW DRUG APPLICATIONS

Much of the general information provided in this guidance is applicable to abbreviated new drugs (ANDAs). However, depending upon the availability of significant information on, and the complexity of, these drug products/dosage forms, the amount of information necessary to support these applications may vary from that proposed for NDAs. This section is intended to provide specific recommendations on abbreviated applications.

A. Drug Substance Stability Data Submission

For drug products submitted under an ANDA, including antibiotics, supporting information may be provided directly to the drug product ANDA or by reference to an appropriately referenced drug master file (DMF). Publications may be provided or referenced as supportive information. For ANDA bulk drug substances, stability data should be generated on a minimum of one pilot-scale batch. All batches should be made using equipment of the same design and operating principle as the manufacturing-scale production equipment with the exception of capacity. For ANDA bulk drug substances produced by fermentation, stability data should be provided on three production batches, at least two of which should be generated from different starter cultures.

B. Drug Substance Testing

A program for stability assessment may include storage at accelerated, long-term, and, if applicable, intermediate stability study storage conditions (refer to IV.G. of the ICH Q1A Guidance and Section II.A. of this guidance). Stability samples should be stored in the bulk storage container equivalent (e.g., same composition and type of container, closure and liner, but smaller in size).

If not previously generated or available by reference, stress testing studies should be conducted to establish the inherent stability characteristics of the drug substance, and support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual drug substance, type of drug product and available supporting information. Any necessary testing may be carried out as described in Section II.A.

C. Drug Product

Original ANDAs should contain stability data generated under the long-term and accelerated stability storage conditions delineated in V.E. of the ICH Q1A guidance (Section II.B. of this guidance). The data package for ANDAs (e.g., number of batches, length of studies needed at submission and at approval, and accelerated, intermediate and long-term stability data) should be based on several factors, including the complexity of the dosage form, the existence of a significant body of information for the dosage form, and the existence of an approved application for a particular dosage form.

D. ANDA Data Package Recommendations

For *Simple Dosage Forms* the following stability data package is recommended:

- Accelerated stability data at 0, 1, 2, and 3 months. A tentative expiration dating period of up to 24 months will be granted based on satisfactory accelerated stability data unless not supported by the available long-term stability data.

- Long-term stability data (available data at the time of original filing and subsequent amendments).
- A minimum of one batch; pilot scale.
- Additional stability studies (12 months at the intermediate conditions, or long-term data through the proposed expiration date) if *significant change* is seen after 3 months during the accelerated stability study. The tentative expiration dating period will be determined based on the available data from the additional study.

E. Exceptions to the ANDA Data Package Recommendations

The following may be considered exceptions to the general ANDA recommendations:

- Complex dosage forms, such as modified-release products, transdermal patches, metered-dose inhalers.
- Drug products without a significant body of information.
- New dosage forms submitted through the ANDA suitability petition process (Q1C applications).
- Other exceptions may exist and should be discussed with the Office of Generic Drugs.

An ANDA that is determined to be one of the above categories should contain a modified ICH Q1A stability data package, including:

- 3-month accelerated stability studies.
- Long-term stability studies (available data at the time of original filing and subsequent amendments). The expiration dating period for complex dosage forms will be determined based on available long-term stability data submitted in the application.
- A minimum of three batches manufactured in accordance with the ICH Q1A batch size recommendations (refer to V.B. of the ICH Q1A guidance and Section II.B. of this guidance).
- Additional stability studies (12 months at the intermediate conditions or long-term stability testing through the proposed expiration date) if significant change is seen after 3 months during the accelerated stability studies (the tentative expiration dating period will be determined based on the available data from the additional studies).

F. Data Package for Approval

Full-term stability testing of the primary stability batch(es) is suggested. However, in the absence of full-term stability data for the drug product, adequate accelerated stability data combined with available long-term data can be used as the basis for granting a tentative expiration dating period. The batch(es) used for stability testing should comply fully with the proposed specifications for the product and be packaged in the market package, and the release assay should be within reasonable variation (taking into account inherent assay variability) from the labeled strength or theoretical strength of the reference listed drug. If formulated with an overage, the overage should be justified as necessary to match that of the reference listed drug.

Other supportive stability data may be submitted on drug product batches that may or may not meet the above criteria. Data on relevant research batches, investigational formulations, alternate container/closure systems, or from other related studies may also be submitted to support the stability of the drug product. The supportive stability data should be clearly identified.

G. Stability Study Acceptance

If the results are satisfactory, a tentative expiration dating period of up to 24 months at the labeled storage conditions may be granted. Where data from accelerated studies are used to project a tentative expiration dating period that is beyond a date supported by actual long-term studies on production batches, the application should include a commitment to conduct long-term stability studies on the first three production batches and annual batches until the tentative expiration dating period is verified, or the appropriate expiration dating period is determined. Extension of the tentative expiration dating period should be based on data generated on at least three production batches tested according to the approved protocol outlined in the stability commitment. Reporting of the data should follow Section VI. of this guidance.

ANDAs withdrawn prior to publication of this guidance should not normally have to include stability data in conformance with the guidance upon resubmission if the original application was withdrawn due to non-stability related issues. However, if new stability studies are conducted to support the submission, such studies should be conducted as recommended in the guidance.

IV. STABILITY TESTING FOR INVESTIGATIONAL NEW DRUG APPLICATIONS

Much of the following information is taken from the guidance for industry, *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic Biotechnology-derived Products* (November 1995).

The regulation at 312.23(a)(7) emphasizes the graded nature of manufacturing and controls information. Although in each phase of the investigation, sufficient information should be submitted to ensure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to achieve that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. Therefore, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.

It is recognized that modifications to the method of preparation of the new drug substance and dosage form, and even changes in the dosage form itself, are likely as the investigation progresses. In an initial phase 1 CMC submission, the emphasis should generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study. The identification of a safety concern or insufficient data to make an evaluation of safety are the only reasons for placing a trial on clinical hold based on the CMC section.

A. Phase 1

Information to support the stability of the drug substance during the toxicologic studies and the proposed clinical study(ies) should include the following: a brief description of the stability study and the test methods used to monitor the stability of the drug substance and preliminary tabular data based on representative material. Neither detailed stability data nor the stability protocol need to be submitted.

Information to support the stability of the drug product during the toxicologic studies and the proposed clinical study(ies) should include the following: a brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the proposed container/closure system and storage conditions and preliminary tabular data based on representative material. Neither detailed stability data nor the stability protocol need to be submitted.

When significant decomposition during storage cannot be prevented, the clinical trial batch of drug product should be retested prior to the initiation of the trial and information should be submitted to show that it will remain stable during the course of the trial. This information should be based on the limited stability data available when the trial starts. Impurities that increase during storage may be qualified by reference to prior human or animal data.

B. Phase 2

Development of drug product formulations during phase 2 should be based in part on the accumulating stability information gained from studies of the drug substance and its formulations.

The objectives of stability testing during phases 1 and 2 are to evaluate the stability of the investigational formulations used in the initial clinical trials, to obtain the additional information needed to develop a final formulation, and to select the most appropriate container and closure (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 during phase 2. Stability studies on these formulations should be well underway by the end of Phase 2. At this point the stability protocol for study of both the drug substance and drug product should be defined, so that stability data generated during phase 3 studies will be appropriate for submission in the drug application.

C. Phase 3

In stability testing during phase 3 IND studies, the emphasis should be on testing final formulations in their proposed market packaging and manufacturing site based on the recommendations and objectives of this guidance. It is recommended that the final stability protocol be well defined prior to the initiation of phase 3 IND studies. In this regard, consideration should be given to establish appropriate linkage between the preclinical and clinical batches of the drug substance and drug product and those of the primary stability batches in support of the proposed expiration dating period. Factors to be considered may include, for example, source, quality and purity of various components of the drug product, manufacturing process of and facility for the drug substance and the drug product, and use of same containers and closures.

V. APPROVED STABILITY PROTOCOL

A. Stability Protocol

An *approved stability protocol* is a detailed plan described in an approved application that is used to generate and analyze stability data to support the retest period for a drug substance or the expiration dating period for a drug product. It also may be used in developing similar data to support an extension of that retest or expiration dating period via annual reports under 21 CFR 314.70(d)(5). If needed, consultation with FDA is encouraged prior to the implementation of the stability protocol.

To ensure that the identity, strength, quality, and purity of a drug product are maintained throughout its expiration dating period, stability studies should include the drug product packaged in the proposed containers and closures for marketing as well as for physician and/or promotional samples. The stability protocol may also include an assessment of the drug product in bulk containers to support short-term storage prior to packaging in the market container.

The stability protocol should include methodology for each parameter assessed during the stability evaluation of the drug substance and the drug product. The protocol should also address analyses and approaches for the evaluation of results and the determination of the expiration dating period, or retest period. The stability-indicating methodology should be validated by the manufacturer and described in sufficient detail to permit validation and/or verification by FDA laboratories.

The stability protocol for both the drug substance and the drug product should be designed in a manner to allow storage under specifically defined conditions. For the drug product, the protocol should support a labeling storage statement at CRT, refrigerator temperature, or freezer temperature. See Sections II.B.5 and 6.

A properly designed stability protocol should include the following information:

- Technical grade and manufacturer of drug substance and excipients
- Type, size, and number of batches
- Type, size, and source of containers and closures
- Test parameters
- Test methods
- Acceptance criteria
- Test time points
- Test storage conditions
- Container storage orientations
- Sampling plan
- Statistical analysis approaches and evaluations
- Data presentation
- Retest or expiration dating period (proposed or approved)

- Stability commitment

The use of alternative designs, such as bracketing and matrixing, may be appropriate (see Sections VII.G. and H.).

At the time of a drug application approval, the applicant has probably not yet manufactured the subject drug product repeatedly on a production scale or accrued full long-term data. The expiration dating period granted in the original application is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA, or on acceptable accelerated data for an ANDA. It is often derived from pilot-scale batches of a drug product or from less than full long-term stability data. An expiration dating period assigned in this manner is considered tentative until confirmed with full long-term stability data from at least three production batches reported through annual reports. The stability protocol approved in the application is then crucial for the confirmation purpose.

B. Stability Commitment

A stability commitment is acceptable when there are sufficient supporting data to predict a favorable outcome with a high degree of confidence, such as when an application is approved with stability data available from pilot-plant batches, when a supplement is approved with data that do not cover the full expiration dating period, or as a condition of approval. This commitment constitutes an agreement to:

1. Conduct and/or complete the necessary studies on the first three production batches and annual batches thereafter of each drug product, container, and closure according to the approved stability protocol through the expiration dating period.

2. Submit stability study results at the time intervals and in the format specified by the FDA, including the annual batches.

3. Withdraw from the market any batches 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 appropriate chemistry team and provide justification for the continued distribution of that batch . The change or deterioration in the distributed drug or biological product must be reported under 21 CFR 314.81(b)(1)(ii) or 21 CFR 601.14, respectively.

For postapproval changes, items 2 and 3 remain the same and item 1 becomes:

1. Conduct and/or complete the necessary studies on the appropriate number of batches. The amount of stability data supplied will depend on the nature of the change being made. Applicants may determine the appropriate data package by consulting the PostApproval Changes section of this guidance (Section IX.) and in consultation with the appropriate chemistry review team.

The approved stability protocol should be revised as necessary to reflect updates to USP monographs or the current state-of-the-art regarding the type of parameters monitored, acceptance criteria of such parameters, and the test methodology used to assess such parameters. However, other modifications are discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches. Once a sufficient database is established from several production batches to confirm the originally approved expiration dating period, it may be appropriate to modify the stability protocol. See Section IX.J.

VI. REPORTING STABILITY DATA

A. General

Stability data should be included in the application (NDA, ANDA, BLA, PLA, IND, supplement) they are intended to support. The extent of stability data expected at the time of submission is discussed at length throughout this guidance. Additional data from ongoing studies and regular annual batches should be included in the application's annual report.

Annual reports should include new or updated stability data generated in accordance with the approved stability protocol. These data may include accelerated and long-term studies for each product to satisfy the standard stability commitment made in the original or supplemental application, including the annual batch(es), and to support postapproval changes. The data should be presented in an organized, comprehensive, and cumulative format.

B. Content of Stability Reports

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

1. General Product Information

- Name, source, manufacturing sites, and date of manufacture of drug substance and drug or biological product.
- 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, the formulation number is acceptable.)
- Composition, type, source, size, and adequate description of container and closure. Stuffers, seals, and desiccants should also be identified.

2. Specifications and Test Methodology Information

- Physical, chemical, and microbiological attributes and regulatory specifications (or specific references to NDA, BLA, PLA, or USP).
- Test methodology used (or specific reference to IND, ANDA, NDA, BLA, PLA prior submissions, or USP) for each sample tested.
- Information on accuracy, precision, and suitability of the methodology (cited by reference to

appropriate sections).

- Where applicable, a description of the potency test(s) for measuring biological activity, including specifications for potency determination.

3. Study Design and Study Conditions

- Description of the sampling plan, including:
  - Batches and number selected.
  - Container and closures and number selected.
  - Number of dosage units selected and whether tests were conducted on individual units or on composites of individual units.
  - Sampling time points.
  - Testing of drug or biological products for reconstitution at the time of reconstitution (as directed on the labeling) as well as through their recommended use periods.
- Expected duration of the study.
- Conditions of storage of the product under study (e.g., temperature, humidity, light, container orientation).

4. Stability Data/Information

- Batch number (research, pilot, production) and associated manufacturing date.
- For antibiotic drug products, the age of the bulk active drug substance(s) used in manufacturing the batch.
- Analytical data, source of each data point, and date of analysis (e.g., batch, container, composite, etc). Pooled estimates may be submitted if individual data points are provided.
- Individual data as well as mean and standard deviation should be reported.
- Tabulated data by storage condition.
- Summary of information on previous formulations during product development. This summary may be referenced (if previously submitted) and should include other containers and closures investigated.

5. Data Analysis

The following data analysis of quantitative parameters should be provided:

- Evaluation of data, plots, and/or graphics.
- Documentation of appropriate statistical methods and formulas used.
- Results of statistical analysis and estimated expiration dating period.
- Results of statistical tests used in arriving at microbiological potency estimates.

6. Conclusions

- Proposed expiration dating period and its justification.
- Regulatory specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted).

C. Formatting Stability Reports

Submitted information should be cumulative and in tabular form. Examples are provided on the following list and in Table 4.

Summary Of Stability Studies For Drug Product X

Study Number
Drug Product Batch #/Control #*, **
Formulation Code/No
Dosage and Strength
Batch Type and Size
Storage Conditions
Drug Substance Mfg/Site/Batch#
Length of Study

Container Composition/Supplier
Closure Composition/Supplier
Seal/Supplier
Mfg/Site/Date
Packager/Site/Date
Location of Data in Application
Specs Failures
Reporting Period

*Batches Used in Clinical Studies and Biostudies (Specify)
**Batches of Different Formulation

Table 4: Model Stability Data Presentation

<u>Summary of Stability Studies for Drug Product X</u>

Product Name
Study Number
Formulation Code/Number
Dosage and Strength
Drug Product Batch Number/Control Number[a,b]
Batch Type and Size
Drug Product Manufacturer/Site/Date
Drug Substance Manufacturer/Site/Batch Number
Container Composition/Supplier
Closure Composition/Supplier
Seal/Supplier
Packager/Site/Date
Sampling Plan
Specifications and Test Methods
Storage Conditions
Length of Study
Reporting Period
Location of Data in Application
Summary of Data
Data Analysis
Conclusions

[a] Batches used in clinical studies and biostudies (specify).
[b] Batches of different formulations.

Table 4: (cont.)

Stability Raw Data for Drug Product X, Batch Y

Product Name/Strength
Batch Number
Date Manufactured
Date Packaged
Storage Condition

Study Number
Batch Size
Manufacturer/Site
Packager/Site
Storage Orientation

Purpose of Study
Date Study Started
Container/Size/Supplier
Closure Supplier
Seal Supplier

Drug Substance Manufacturer/Site/Batch Number
Approved/Proposed Expiration Dating Period

Attributes	Method	Specification	Time (Months)							
	SOP #	(Low/High)	0	3	6	9	12	18	24	etc.
Appearance										
Assay										
Degradation Product A										
Degradation Product B										
Degradation Product C										
etc.										

VII. SPECIFIC STABILITY TOPICS

A. Mean Kinetic Temperature

1. Introduction

Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act states that a drug shall be deemed to be adulterated if the facilities or controls used for holding drugs do not conform to or are not operated or administered in conformity with good manufacturing practice to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess. This applies to all persons engaged in manufacture and holding, i.e., storage, of drugs.

Current good manufacturing practices (CGMP) regulations applicable to drug manufacturers (21 CFR 211.142) state that written procedures describing the warehousing of drug products shall be established and followed. These regulations also state that such procedures shall include instructions for the storage of drug products under appropriate conditions of temperature, humidity, and light so the identity, strength, quality, and purity of the drug products are not affected.

The regulation governing state licensing of wholesale prescription drug distributors (21 CFR 205.50 (c)) states that all prescription drugs shall be stored at appropriate temperatures and under appropriate conditions in accordance with requirements, if any, in the labeling of such drugs, or with requirements in the current edition of an official compendium, such as the USP/NF. The regulation also states that if no storage requirements are established for a prescription drug, the drug may be held at CRT, as defined in an official compendium, to help ensure that its identity, strength, quality and purity are not adversely affected (21 CFR 205.50 (c)(1)).

Mean kinetic temperature (MKT) [4] is defined as the isothermal temperature that corresponds to the kinetic effects of a time-temperature distribution. The Haynes formula can be used to calculate the MKT. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes derived his formula. Thus, MKT is the single calculated temperature that simulates the nonisothermal effects of storage temperature variations. This section of the guidance explains how to calculate MKT. It also recommends a course of action should a facility containing products that are labeled for CRT storage fail to maintain the drugs at appropriate temperature conditions as defined in this guidance. Because MKT is intended to provide guidance on temperature control of drug storage facilities and is not correlated to any specific lot of drug product in the storage facility, an MKT in excess of 25°C does not, on its own, infer that CGMPs have been violated.

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[4] J.D. Haynes,"Worldwide Virtual Temperatures for Product Stability Testing", *J. Pharm. Sci.*, Vol. 60, No. 6, 927 (June 1971).

2. Calculation

There are a variety of ways to approximate a MKT. The FDA recommends that, for manufacturers, repackagers, and warehouses, all data points obtained be inserted directly into the MKT equation. A minimum of weekly high and low readings is recommended, and more rigorous approximations using daily highs and lows or even more frequent temperature readings would be acceptable. Storage temperatures may be obtained using automated recording devices, chart recorders, or a high-low thermometer.

The temperature readings (minimum of 104 weekly high and low readings) would be inserted into the MKT equation to calculate a yearly MKT. The yearly MKT for the preceding twelve months should be calculated every month. At times when no drugs are stored in a facility, those intervals should not be used in MKT calculations. The MKT equation is shown below:

$$T_k = \frac{\frac{-\Delta H}{R}}{\ln\left(\frac{e^{-\frac{\Delta H}{RT_{1_H}}} + e^{-\frac{\Delta H}{RT_{1_L}}} + \cdots + e^{-\frac{\Delta H}{RT_{n_H}}} + e^{-\frac{\Delta H}{RT_{n_L}}}}{2n}\right)}$$

Where:

T_k= the mean kinetic temperature in ^{o}K
ΔH= the heat of activation, 83.144 kJ•mole^{-1}
R = the universal gas constant, 8.3144 x 10^{-3} kJ•mole^{-1}•^{o}K^{-1}
T_{1H}= the high temperature in ^{o}K during the 1st week
T_{1L}= the low temperature in ^{o}K during the 1st week
T_{nH}= the high temperature in ^{o}K during the nth week
T_{nL}= the low temperature in ^{o}K during the nth week
n = the total number of weeks (i.e. 52)
T = absolute temperature in ^{o}K
^{o}K = ^{o}C (Celsius) + 273.2
^{o}K = [(^{o}F (Fahrenheit) -32)•0.555] + 273.2

Note that 83.144 kJoules/mol is an average value based upon many common organic reactions. Since $\Delta H/R = 10{,}000\,^{\circ}K$, the above equation can be simplified as:

$$T_k = \frac{-10{,}000}{\ln\left(\frac{e^{-\frac{10{,}000}{T_{1_H}}} + e^{-\frac{10{,}000}{T_{1_L}}} + \cdots + e^{-\frac{10{,}000}{T_{n_H}}} + e^{-\frac{10{,}000}{T_{n_L}}}}{2n}\right)}$$

3. Application

Any time the yearly MKT of a facility approaches 25ºC, the occurrence should be documented, the cause for such an occurrence should be investigated, and corrective actions should be taken to ensure that the facility is maintained within the established conditions for drug product storage. FDA recognizes that, when the yearly MKT of a facility begins to exceed 25ºC, it may not necessarily have an impact on products that have been stored for less than one year at the time, but should be a warning that the facility itself may not be under adequate control.

In addition, whenever the recorded temperature (as opposed to the calculated MKT) exceeds the allowable excursions of 15-30ºC in a facility that contains drugs labeled for storage at CRT, the occurrence should be documented. The cause for such an occurrence should be investigated, and corrective actions taken to ensure that the facility is maintained within the established conditions for drug product storage. The FDA recognizes that brief spikes outside of 15-30ºC may, in fact, be expected from time to time in the real world and may not necessarily have an impact on product quality. However, depending on the duration and extent of such an exposure and the dosage form, it may be necessary to determine if the product quality has been adversely affected.

B. Container/Closure

Stability data should be developed for the drug product in each type of immediate container and closure proposed for marketing, promotion, or bulk storage. The possibility of interaction between the drug and the container and closure and the potential introduction of extractables into the drug product formulations during storage should be assessed during container/closure qualification studies using sensitive and quantitative procedures. These studies are recommended even if the container and closure meet compendial suitability tests, such as those outlined in the USP for plastic containers and elastomeric or plastic closures. A draft guidance is available on this topic entitled *Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics* (June 1997).

1. Container and Closure Size

Stability data for a given strength may be bracketed by obtaining data for the smallest and the largest container and closure to be commercially marketed, provided that the intermediate container and closure is of comparable composition and design (Section VII.G.).

Physician and/or promotional samples that are in different containers and closures or sizes from the marketed package should be included in the stability studies. Samples in similar container closure systems may be included in bracketing or matrixing studies (Section VII.H.).
For solid oral dosage forms packaged in large containers (i.e., those not intended for direct distribution to the patient) full stability studies should be performed if further packaging by health institutions or contract packagers is anticipated. Samples for stability testing at different time points may be taken from the same container. Stability data also may be necessary when the finished dosage form is stored in interim bulk containers prior to filling into the marketed package. If the dosage form is stored in bulk containers for over 30 days, real-time stability data under

specified storage conditions should be generated to demonstrate comparable stability to the dosage form in the marketed package. Interim storage of the dosage form in bulk containers should generally not exceed six months. The computation of the expiration dating period of the final marketed product should begin within 30 days of the date of production (see Glossary) of the dosage form, as defined in the section on Computation of Expiration Dating Period (Section VII.F.1.), irrespective of the packaging date. If the dosage form is shipped in bulk containers prior to final packaging, a simulated study may be important to demonstrate that adverse shipping and/or climatic conditions do not affect its stability.

2. Container Orientations

Solutions (i.e., oral, SVPs, LVPs, oral and nasal inhalations, and topical preparations), dispersed systems (oral, MDIs, injectables), and semi-solid drug products (topical, ophthalmics, and otics) should be stored in both the upright and either inverted or on-the-side positions until contact with the container/closure system has been shown not to impact on drug product quality. The comparison between upright and inverted or on-the-side position is important to determine whether contact of the drug product (or solvent) with the closure results in extraction of chemical substances from the closure components or adsorption and absorption of product components into the container/closure. The evaluation should include the set of test parameters that are listed in Considerations for Specific Dosage Forms (Section VIII.). Upright versus inverted/on-the-side stability studies should be performed during the preapproval and postapproval verification stages of the stability program. Once it has been demonstrated that the product in maximum contact with the primary pack does not have a significantly greater impact on drug product quality than the upright orientation, stability studies may be continued only in the most stressful orientation, which is generally the inverted or on-the-side position.

3. Extractables and Adsorption/Absorption of Drug Product Components

Specific extractables testing on a drug product is not recommended. Inverted versus upright stability testing during preapproval and postapproval verification is usually adequate. Extensive testing for extractables should be performed as part of the qualification of the container/closure components, labels, adhesives, colorants and ink (see previously cited packaging guidance for additional information). Such testing should demonstrate that the levels of extractables found during extraction studies, which are generally performed with various solvents, elevated temperatures and prolonged extraction times, are at levels determined to be acceptable, and that those levels will not be approached during the shelf life of the drug product.

Loss of the active drug substance or critical excipients of the drug product by interaction with the container/closure components or components of the drug delivery device is generally evaluated as part of the stability protocol. This is usually accomplished by assaying those critical drug product components, as well as monitoring various critical parameters (e.g., pH, preservative effectiveness). Excessive loss of a component or change in a parameter will result in the failure of the drug product to meet applicable specifications.

C. Microbiological Control and Quality

1. Preservatives Effectiveness

Both sterile and nonsterile drug products may contain preservative systems to control bacteria and fungi that may be inadvertently introduced during manufacturing. Acceptance criteria should be provided as part of the drug product specifications for the chemical content of preservatives at the time of product release and/or through the product shelf life.

The minimum acceptable limit for the content of preservatives in a drug product should be demonstrated as microbiologically effective by performing a microbial challenge assay of the drug formulated with an amount of preservative less than the minimum amount specified as acceptable. This approach provides a margin of safety within the limit and a margin of error for the assays. Additionally, compatibility of the preservative system with the container, closure, formulation and devices (e.g., pumps, injection pens) should be demonstrated over the contact period. Multiple use container systems, for example, containers that are used after the closure is replaced with an applicator or dropper and large bottles containing syrups or suspensions should be tested for the microbiological effectiveness of the preservatives system following simulated uses, including breaches of the container system as permitted in the labeling. USP “Antimicrobial Preservatives-Effectiveness”<51> provides a microbial challenge assay.

For the purpose of approval of drug applications, stability data on pilot-scale batches should include results from microbial challenge studies performed on the drug product at appropriate intervals. Generally, microbial challenge studies conducted initially, annually, and at the end of the expiration dating period are adequate. Chemical assays of preservative content(s) should be performed at all test points.

For postapproval testing, the first three production batches should be tested with a microbial challenge assay at the start and the end of the stability period and at one point in the middle of the stability period if the test period equals or exceeds two years. The first three production batches should be assayed for the chemical content of the preservatives at all appropriate test points. Upon demonstration of chemical content commensurate with microbial effectiveness in the first three production batches, chemical assays may be adequate to demonstrate the maintenance of the specified concentrations of preservatives for subsequent annual batches placed into stability testing.

2. Microbiological Limits for Nonsterile Drug Products

Nonsterile drug products that have specified microbial limits for drug product release should be tested for conformance to the specified limits at appropriate, defined time points during stability studies. The USP provides microbiological test methods for microbial limits and guidance concerning microbiological attributes of nonsterile drug products.

3. Sterility Assurance for Sterile Drug Products

The stability studies for sterile drug products should include data from a sterility test of each batch at the beginning of the test period. Additional testing is recommended to demonstrate maintenance of the integrity of the microbial barrier provided by the container and closure system. These tests should be performed annually and at expiry.

Integrity of the microbial barrier should be assessed using an appropriately sensitive and adequately validated container and closure integrity test. The sensitivity of this test should be established and documented to show the amount of leakage necessary to detect a failed barrier in a container and closure system. The number of samples to be tested should be similar to the sampling requirement provided in current USP "Sterility Tests" <71>. The samples that pass container and closure integrity testing may be used for other stability testing for that specific time point, but should not be returned to storage for future stability testing. Container and closure integrity tests do not replace the current USP "Sterility Tests" <71> or 21 CFR 610.12 for product release.

4. Pyrogens and Bacterial Endotoxins

Drug products with specified limits for pyrogens or bacterial endotoxins should be tested at the time of release and at appropriate intervals during the stability period. For most parenteral products, testing at the beginning and the end of the stability test period may be adequate. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional testing beyond the initial time point. Products containing liquids in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and the end of the stability test period. For test procedures and specifications, refer to the FDA *Guideline on Validation of the Limulus Amoebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*, the USP "Bacterial Endotoxins Test" <85>, and the USP "Pyrogen Test" <151>.

D. Stability Sampling Considerations

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. Therefore, tested batches should be representative in all respects such as formulation, manufacturing site, container and closure, manufacturing process, source and quality of bulk material of the population of all production batches and conform with all quality specifications of the drug product.

The design of a stability study should take into consideration the variability of individual dosage units, of containers within a batch, and of batches to ensure that the resulting data for each dosage unit or container 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 that a future batch would remain within specifications until its expiration date.

1. Batch Sampling

Batches selected for stability studies should optimally constitute a random sample from the population of production batches. In practice, the batches tested to establish the expiration dating period are often made at a pilot plant that may only simulate full-scale production. Future changes in the production process may thus render the initial stability study conclusions obsolete.

At least three batches, preferably more, should be tested to allow an estimate of batch-to-batch variability and to test the hypothesis that a single expiration dating period for all batches is justifiable. Testing of less than three batches does not permit a reliable estimate of batch-to-batch variability unless a significant body of information is available on the dosage form and/or drug product. Although data from more batches will result in a more precise estimate, practical considerations prevent collection of extensive amounts of data. When a significant body of information is not available, testing at least three batches represents a compromise between statistical and practical considerations.

2. Container, Closure, and Drug Product Sampling

Selection of containers, such as bottles, packages, and vials, from the batch chosen for inclusion in the stability study should ensure that the samples represent the batch as a whole. This can be accomplished by taking a random sample of containers from the finished batch, by using a stratification plan whereby at a random starting point every nth container is taken from the filling or packaging line (*n* is chosen such that the sample is spread over the whole batch), or by some other plan designed to ensure an unbiased selection.

Generally, samples to be assayed at a given sampling time should be taken from previously unopened containers. For this reason, at least as many containers should be sampled as the number of sampling times in the stability study.

For products packaged in containers intended for dispensing by a pharmacy to multiple patients, or intended for repackaging or packaged in unit-of-use containers, samples may be taken from previously opened containers. More than one container should be sampled during the stability study. The sampling protocol should be submitted in the drug application.

Dosage units should be sampled from a given container randomly, with each dosage unit having an equal chance of being included in the sample. If the individual units entered the container randomly, then samples may be taken from units at the opening of the container. However, because dosage units near the cap of large containers may have different stability properties than dosage units in other parts of the container, dosage units should be sampled from all parts of the container. For dosage units sampled in this fashion, the location within the container from which the samples were taken should be documented and this information included with the test results.

Unless the product is being tested for homogeneity, 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. If composites are used, their makeup should be described in the stability study report. The same type of composite should be used throughout the stability study. For example, if 20-tablet composites are tested initially, then

20-tablet composites should be used throughout. If a larger sample at a given sampling time is desired, replicated 20-tablet composites should be assayed rather than a single assay of a composite made from more than 20 tablets. An average of these composite values may be used for the release assay. However, the individual assay values should be reported as well. Although other release and stability tests may be performed on these samples (e.g., impurities, preservatives effectiveness), the results of these tests do not need to be subjected to top/middle/bottom comparisons.

Semisolid drug products in sizes that are intended for multiple uses should be tested for homogeneity. Homogeneity testing may be bracketed by container and/or fill size, with testing done only on the smallest and largest marketed package sizes of each strength. Stability protocols should provide for increased testing in the event of homogeneity failures, or following a change in packaging materials or procedures, for example, with a change to a new sealant, or a change in tube crimping procedures. Where the largest marketed size is more than 20 times the smallest, homogeneity testing of an intermediate size is recommended.

Semisolid drug products in sizes that are intended for single use need not be tested for homogeneity.

3. Sampling Time

The sample time points should be chosen so that any degradation can be adequately profiled (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.

Stability testing for long-term studies generally should be performed at three-month intervals during the first year, six-month intervals during the second, and yearly thereafter. For drug products predicted to degrade more rapidly, for example, certain radiopharmaceuticals, the intervals between sampling times should be shortened. Stability testing for accelerated studies generally should be performed at a minimum of four time points, including the initial sampling time.

Freezing samples after sampling for the convenience of scheduling analysis is not an acceptable practice because it may cause delay in finding and responding to out-of-specification test results, or may adversely affect the stability of a product that does not withstand freezing.

The degradation curve is estimated most precisely, in terms of the width of the confidence limit about the mean curve (Figure 1, Section VII.E.2.), 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.

4. Annual Stability Batches

After the expiration dating period has been verified with three production batches, a testing program for an approved drug product should be implemented to confirm on-going stability. For every approved application, at least one batch of every strength in every approved container/closure system, such as bottles or blisters, should be added to the stability program annually in all subsequent years. If the manufacturing interval is greater than one year, the next batch of drug product released should be added to the stability program. Bracketing and matrixing can be used to optimize testing efficiency.

The recommendations in this section do not apply to compressed medical gases, blood, or blood products.

E. Statistical Considerations and Evaluation

1. Data Analysis and Interpretation for Long-term Studies

A stability protocol should describe not only how the stability study is to be designed and carried out, but also the statistical method to be used in analyzing the data. This section describes an acceptable statistical approach to the analysis of stability data and the specific features of the stability study that are pertinent to the analysis. Generally, an expiration dating or retest period should be determined based on statistical analysis of observed long-term data. Limited extrapolation of the real-time data beyond the observed range to extend the expiration dating or retest period at approval time may be considered if it is supported by the statistical analysis of real-time data, satisfactory accelerated data, and other nonprimary stability data.

The methods described in this section are used to establish with a high degree of confidence an expiration dating period during which average drug product attributes such as assay and degradation products of the batch will remain within specifications. This expiration dating period should be applicable to all future batches produced by the same manufacturing process for the drug product.

If an applicant chooses 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 should be considered.[5] In this setting, testing of individual units, rather than composites, may be important.

Applicants wishing to use a statistical procedure other than those discussed in this guidance should consult with the chemistry review team prior to the initiation of the stability study and data analysis.

2. 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 rate of physical, chemical or microbiological changes, but also on the initial average value

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[5] R.G. Easterling, J. Am. Stat. Assoc., “Discrimination Intervals for Percentiles in Regression”, 64, 1031-41, 1969.

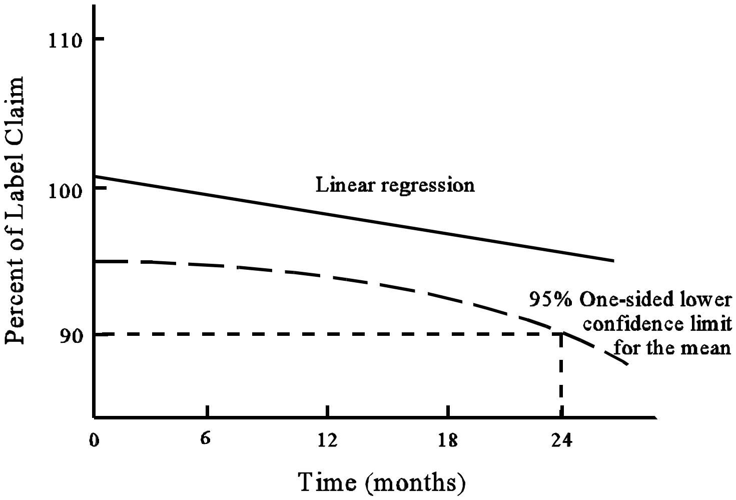
for the batch. Thus, information on the initial value for the batch is relevant to the determination of the allowable expiration dating period and should be included in the stability study report. Percentage of label claim, not percentage of initial average value, is the variable of interest.

The expiration dating period for an individual batch is based on the observed pattern of change in the quantitative attributes (e.g., assay, degradation products) under study and the precision by which it is estimated.

An acceptable approach for analyzing an attribute that is expected to decrease with time is to determine the time at which the 95 percent one-sided lower confidence limit, also known as the 95 percent lower confidence bound, for the estimated curve intersects the acceptable lower specification limit. In the example shown in Figure 1 where the estimated curve is assumed to be linear based on 24 months of real time data and the lower specification limit is assumed to be 90 percent of label claim, an expiration dating period of 24 months could be granted. When analyzing an attribute that is expected to increase with time, the 95 percent one-sided upper confidence limit for the mean is recommended.

When analyzing an attribute with both an upper and a lower specification limit, special cases may lead to application of a two-sided 95 percent confidence limit. For example, although chemical degradation of the active ingredient in a solution product would cause a decrease in the assayed concentration, evaporation of the solvent in the product (through the container/closure) would result in an increase in the concentration. Because both possibilities should be taken into account, two-sided confidence limits would be appropriate. If both mechanisms were acting, the concentration might decrease initially and then increase. In this case, the degradation pattern would not be linear, and more complicated statistical approaches should be considered.

Figure 1: Statistical Analysis of Long-Term Stability Data



If the approach presented in this section is used, average parameters such as assay and degradation products of the dosage units in the batch can be expected to remain within specifications to the end of the expiration dating period at a confidence level of 95 percent. The expiration dating period should not be determined using the point at which 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, in which case the batch average can be expected to remain within specifications at expiration if the fitted least-squares line is used with a confidence level of only 50 percent.

The statistical assumptions underlying the procedures described above, such as 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 violated to some degree. If severe violation of the assumptions in the data is noted, an alternate approach may be necessary to accomplish the objective of determining an expiration dating period with a high degree of confidence.

3. Expiration Dating Period for All Batches

If batch-to-batch variability is small, that is, the relationship between the parameter of interest such as assay or degradation products and time is essentially the same from batch to batch, stability data should be combined into one overall estimate. Combining the data should be supported by preliminary testing of batch similarity.[6] The similarity of the estimated curves among the batches tested should be assessed by applying statistical tests of the equality of slopes and of zero time intercepts. The level o significance of the tests, expressed in the p-value, should be chosen so that the decision to combine the data is made only if there is strong evidence in favor of combining. A p-value of 0.25 for preliminary statistical tests has been recommended.[7] 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 could be pooled. If these tests resulted in p-values less than 0.25, a judgment should be made as to whether pooling could be permitted. The appropriate FDA chemistry review team should be consulted regarding this determination.

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., that the slopes are equal). If so, the data may be combined for the purpose of estimating the common slope. The individual expiration dating period for each batch in the stability study may then be determined by considering the initial values and the common slope using appropriate statistical methodology. If data from several batches are combined, as many batches as feasible should be combined because confidence limits about the estimated curve will become narrower as the number of batches increases, usually resulting in a longer expiration dating period. If it is inappropriate to combine

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[6] K.K. Lin, T-Y.D. Lin, and R.E. Kelley, "Stability of Drugs: Room Temperature Tests", in *Statistics in the Pharmaceutical Industry*, ed. C.R. Buncher and J-Y. Tsay, pp. 419-444, Marcel Dekker, Inc.: New York, 1994.

[7] T. A. Bancroft, "Analysis and Inference for Incompletely Specified Models Involving the Use of Preliminary Test(s) of Significance," *Biometrics*, 20(3), 427-442, 1964.

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

4. Precautions in Extrapolation Beyond Actual Data

The statistical methods for determining an expiration dating period beyond the observed range of time points are the same as for determining an expiration dating period within the observed range. The a priori correctness of the assumed pattern of change as a function of time is crucial in the case of extrapolation beyond the observed range. When estimating a line or curve of change within the observed range of data, the data themselves provide a check on the correctness of the assumed relationship, and statistical methods may be applied to test the goodness of fit of the data to the line or curve. No such internal check is available beyond the range of observed data. For example, if it has been assumed that the relationship between log assay and time is a straight line when, in fact, it is a curve, it may be that within the range of the observed data, the true curve is close enough to a straight line that no serious error is made by approximating the relationship as a straight line. However, beyond the observed data points, the true curve may diverge from a straight line enough to have a significant effect on the estimated expiration dating period.

For extrapolation beyond the observed range to be valid, the assumed change 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 as soon as these data become available.

F. Expiration Dating Period/Retest Period

1. Computation of Expiration Date

The computation of the expiration dating period of the drug product should begin no later than the time of quality control release of that batch, and the date of release should generally not exceed 30 days from the production date, regardless of the packaging date. The data generated in support of the assigned expiration dating period should be from long-term studies under the storage conditions recommended in the labeling. If the expiration date includes only a month and year, the product should meet specifications through the last day of the month.

In general, proper statistical analysis of long-term stability data collected, as recommended in Section VII.E. and exemplified in Figure 1, should support at least a one-year expiration dating period. Exceptions do exist, for example, with short half-life radioactive drug products.

If the production batch contains reprocessed material, the expiration dating period should be computed from the date of manufacture of the oldest reprocessed material used.

a. Extension of Expiration Dating Period

An extension of the expiration dating period based on full long-term stability data obtained from at least three production batches in accordance with a protocol approved in the application may be described in an annual report (21 CFR 314.70(d)(5). The expiration dating period may be extended in an annual report only if the criteria set forth in the approved stability protocol are met in obtaining and analyzing data, including statistical analysis, if appropriate.

Alternatively, if the stability study on at least three pilot-scale batches is continued after the NDA/BLA approval, it is feasible to extend the tentative expiration dating period based on full long-term data obtained from these batches in accordance with the approved protocol, including statistical analysis if appropriate, through a prior approval supplement. However, the expiration dating period thus derived remains tentative until confirmed with full long-term data from at least three production batches.

Unless a new stability protocol has been adopted via a prior approval supplement before the change is made, stability protocols included in drug applications prior to the 1985 revisions to the NDA regulations (50 FR 7452) may not support the extension of expiration dating periods through annual reports. If the data are obtained under a *new* or *revised* stability protocol, a prior approval supplement under 21 CFR 314.70(b) or (g) or 21 CFR 601.12 should be submitted to extend the expiration dating period.

b. Shortening of Expiration Dating Period

When warranted, a previously approved expiration dating period may be shortened via a changes-being-effected supplement (21 CFR 314.70(c)(1) or 21 CFR 601.12). The supplemental application should provide pertinent information and the data that led to the shortening of the expiration dating period. The expiration dating period should be shortened to the nearest available real-time long-term test point where the product meets acceptance criteria. The expiration dating period thus derived should be applied to all subsequent production batches and may not be extended until the cause for the shortening is fully investigated, the problem is resolved, and satisfactory stability data become available on at least three new production batches to cover the desired expiration dating period and are submitted in a changes-being-effected supplement.

2. Retest Period for Drug Substance

A retest period for a drug substance may be established based on the available data from long-term stability studies and, as such, can be longer than 24 months if supported by data. A retest date should be placed on the storage container and on the shipping container for a bulk drug substance. A drug substance batch may be used without retest during an approved retest period. However, beyond the approved retest period, any remaining portion of the batch should be retested immediately before use. Retest of different portions of the same batch for use at different times as needed is acceptable, provided that the batch has been stored under the defined conditions, the test methods are validated and stability-indicating, and all stability-related attributes are tested and test results are satisfactory.

Satisfactory retest results on a drug substance batch after the retest date do not mean that the retest period can be extended for that batch or any other batch. The purpose of retest is to qualify a specific batch of a drug substance for use in the manufacture of a drug product, rather than to recertify the drug substance with a new retest date. To extend the retest period, full long-term data from a formal stability study on three production batches using a protocol approved in an application or found acceptable in a DMF should be provided.

Similar to the extension of an expiration dating period for a drug product, a retest period for a drug substance may be extended beyond what was approved in the original application. This can be achieved through an annual report based on full long-term stability data (i.e., covering the desired retest period on three production batches using an approved stability protocol).

In a case where testing reveals a limited shelf-life for a drug substance, it may be inappropriate to use a retest date. An expiration dating period, rather than a retest period, should be established for a drug substance with a limited shelf-life (e.g., some antibiotics, biological substances).

3. Holding Times for Drug Product Intermediates

Intermediates such as blends, triturates, cores, extended-release beads or pellets may be held for up to 30 days from their date of production without being retested prior to use. An intermediate that is held for longer than 30 days should be monitored for stability under controlled, long-term storage conditions for the length of the holding period. In addition, the first production batch of the finished drug product manufactured with such an intermediate should be monitored on long-term stability. When previous testing of an intermediate or the related drug product batches suggests that an intermediate may not be stable for 30 days, the holding time should be kept to a minimum and qualified by appropriate stability testing.

The frequency of testing of an intermediate on stability is related to the length of the holding time. Where practical, testing should be done at a minimum of three time points after the initial testing of an intermediate. At a minimum, all critical parameters should be evaluated at release of an intermediate and immediately prior to its use in the manufacture of the finished drug product.

In the event that the holding time for an intermediate has not been qualified by appropriate stability evaluations, the expiration date assigned to the related finished drug product batch should be computed from the quality control release date of the intermediate if this date does not exceed 30 days from the date of production of the intermediate. If the holding time has been qualified by appropriate stability studies, the expiration date assigned to the related finished drug product can be computed from its quality control release date if this release date does not exceed 30 days from the date that the intermediate is introduced into the manufacture of the finished drug product.

G. Bracketing

1. General

The use of reduced stability testing, such as a bracketing design, may be a suitable alternative to a full testing program where the drug is available in multiple sizes or strengths. This section discusses the types of products and submissions to which a bracketing design is applicable and the types of factors that can be bracketed. Applicants are advised to consult with the FDA when questions arise.

2. Applicability

The factors that may be bracketed in a stability study are outlined in ICH Q1A and described in further detail below. The types of drug products and the types of submissions to which bracketing design can be applied are also discussed.

a. Types of drug product

Bracketing design is applicable to most types of drug products, including immediate- and modified-release oral solids, liquids, semi-solids, injectables. Certain types of drug products, such as metered-dosed inhalers (MDIs), dry powder inhalers (DPIs) and transdermal delivery systems (TDSs), may not be amenable to, or may need additional justification for, bracketing design.

b. Factors

Where a range of container/fill sizes for a drug product of the same strength is to be evaluated, bracketing design may be applicable if the material and composition of the container and the type of closure are the same throughout the range. In a case where either the container size or fill size varies while the other remains the same, bracketing design may be applicable without justification. In a case where both container size and fill size vary, bracketing design is applicable if appropriate justification is provided. Such justification should demonstrate that the various aspects (surface area/volume ratio, dead-space/volume ratio, container wall thickness, closure geometry) of the intermediate sizes will be adequately bracketed by the extreme sizes selected.

Where a range of dosage strengths for a drug product in the same container/closure (with identical material and size) is to be tested, bracketing design may be applicable if the formulation is identical or very closely related in components/composition. Examples for the former include a tablet range made with different compression weights of a common granulation, or a capsule range made by filling different plug fill weights of the same composition into different size capsule shells. The phrase *very closely related formulation* means a range of strengths with a similar, but not identical, basic composition such that the ratio of active ingredient to excipients remains relatively constant throughout the range (e.g., addition or deletion of a colorant or flavoring).

In the case where the amount of active ingredient changes while the amount of each excipient or the total weight of the dosage unit remains constant, bracketing may not be applicable unless justified. Such justification may include a demonstration of comparable stability profile among the different strengths based on data obtained from clinical/development batches, primary stability batches, and/or production batches in support of primary stability batches, commitment batches, and/or annual batches and batches for postapproval changes, respectively. With this approach, the formulations should be identical or very closely related, and the container/closure system should be the same between the supportive batches and the batches for which the bracketing design is intended.

If the formulation is significantly different among the different strengths (e.g., addition or deletion of an excipient, except colorant or flavoring), bracketing is generally not applicable.

Due to the complexity in product formulation, applicants are advised to consult the appropriate chemistry review team in advance when questions arise in the above situations or where justification is needed for bracketing design.

In the case where the strength and the container and/or fill size of a drug product both vary, bracketing design may be applicable if justified.

c. Types of submissions

A bracketing design may be used for primary stability batches in an original application, postapproval commitment batches, annual batches, or batches intended to support supplemental changes. Bracketing design should not be applied to clinical batches during the IND stages when the product is still under development. Where additional justification is needed for applying a bracketing design, product stability should be demonstrated using supportive data obtained from clinical/development or NDA batches, commitment batches, or production batches. Before a bracketing protocol is applied to primary stability batches to support an application, the protocol should be endorsed by Agency chemistry staff via an IND amendment, an end-of-phase 2 meeting, or prior to submission of an ANDA. Bracketing protocols to be applied to postapproval commitment batches and annual batches, if proposed, will be approved as part of the original application.

A bracketing design that is not contained in the approved protocol in the application is subject to supplemental approval (21 CFR 314.70(b)(2)(ix)) (601.12). If the new bracketing design is used to generate stability data to support two different chemistry, manufacturing or controls changes, the two proposed changes could be combined into one prior-approval supplement even though the latter may otherwise qualify for a changes-being-effected supplement or annual report under 314.70 (c) or (d) or 601.12, or relevant SUPAC guidances. Alternatively, the applicant may consult the appropriate Agency review staff through general correspondence regarding the acceptability of the new bracketing design prior to the initiation of the stability studies, and subsequently submit the data to support the proposed change through the appropriate filing mechanism.

3. Design

A bracketing protocol should always include the extremes of the intended commercial sizes and/or strengths. Physician samples or bulk pharmacy packs intended to be repackaged should be excluded from the bracketing protocol for commercial sizes, but could be studied under their own bracketing protocols, if applicable. Where a large number, for example four or more, of sizes/strengths is involved, the inclusion of the one batch each of the intermediates or three batches of the middle size/strength in the bracketing design is recommended. Where the ultimate commercial sizes/strengths differ from those bracketed in the original application, a commitment should be made to place the first production batches of the appropriate extremes on the stability study postapproval. Such differences should, however, be justified. Where additional justification for the bracketing design is needed in the original application, one or more of the first production batches of the intermediate(s) should be placed on the postapproval long-term stability study.

An example of bracketing design is presented in Table 5, where both strengths and container/fill sizes are bracketed in one protocol and "X" denotes the combination of strength and container/fill size to be placed on stability study. In this hypothetical situation, the capsule dosage form is available in three different strengths made from a common granulation and packaged in three different sizes of HDPE bottles with different fills: 30 counts, C1; 100 counts, C2; and 200 counts, C3. The surface area/volume ratio, dead space/volume ratio, container wall thickness, and closure performance characteristics are assumed to be proportional among the three container/fill sizes for each strength of the capsules.

Table 5: Bracketing Example

Batch	1									2									3								
Strength	100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Sample on Stability	X		X				X		X	X		X				X		X	X		X				X		X

4. Data evaluation

The stability data obtained under a bracketing protocol should be subjected to the same type of statistical analysis described in Section VII.E. The same principle and procedure on poolability should be applied (i.e., testing data from different batches for similarity before combining them into one overall estimate). If the statistical assessments of the extremes are found to be dissimilar, the intermediate sizes/strengths should be considered to be no more stable than the least stable extreme.[8]

H. Matrixing

1. General

The use of reduced stability testing, such as a matrixing design, may be a suitable alternative to a full testing program where multiple factors involved in the product are being evaluated. The principle behind matrixing is described in ICH Q1A. This section provides further guidance on when it is appropriate to use matrixing and how to design such a study. Consultation with FDA is encouraged before the design is implemented.

2. Applicability

The types of drug products and the types of submissions to which matrixing design can be applied are the same as described for bracketing above. The factors that can be matrixed with or without justification and those that should not be matrixed are discussed below. Additionally, data variability and product stability, as demonstrated through previous supportive batches, should be considered when determining if matrixing can be applied to the batches of interest.

a. Types of drug product

Matrixing design is applicable to most types of drug products, including immediate- and modified-release oral solids, liquids, semisolids, injectables. Certain types of drug products such as MDIs, DPIs, and TDSs may not be amenable to, or may need additional justification for, matrixing design.

b. Factors

Some of the factors that can be matrixed include batches, strengths with identical formulation, container sizes, fill sizes, and intermediate time points. With justification, additional factors that can be matrixed include strengths with closely related formulation, container and closure suppliers, container and closure systems, orientations of container during storage, drug substance manufacturing sites, and drug product manufacturing sites. For example, to justify matrixing across HDPE bottles and blister packs, a tablet dosage form could be shown not to be sensitive to moisture, oxygen, or light (through stressed studies, including open-dish experiments) and that it is so stable that the protective nature of the container/closure system made little or no difference in the product stability (through supportive data). Alternatively, it could be demonstrated, if

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[8] For additional information on bracketing studies, see W.R. Fairweather, T.-Y. D. Lin, and R. Kelly, "Regulatory, Design, and Analysis Aspects of Complex Stability Studies," *J. Pharm. Sci.*, **84**, 1322-1326, 1995.

appropriate, that there is no difference in the protective nature between the two distinctively different container/closure systems. The justification is needed to ensure that the matrixing protocol would lead to a successful prediction of the expiration dating period when two otherwise different container/closure systems are studied together.

Factors that should not be matrixed include initial and final time points, attributes (test parameters), dosage forms, strengths with different formulations (i.e., different excipients or different active/excipient ratios, and storage conditions).

c. Data variability and Product Stability

The applicability of matrixing design to primary stability batches depends on the product stability and data variability demonstrated through clinical or developmental batches. Data variability refers to the variability of supportive stability data within a given factor (i.e., batch-to-batch, strength-to-strength, size-to-size) and across different factors (e.g., batch vs strength, strength vs size). It is assumed that there is very little variability in the analytical methods used in the testing of stability samples. Matrixing design is applicable if these supportive data indicate that the product exhibits excellent stability with very small variability. Where the product displays moderate stability with moderate variability in the supportive data, matrixing design is applicable with additional justification. Conversely, if supportive data suggest poor product stability with large variability, matrixing design is not applicable. Similarly, whether or not matrixing design can be applied to postapproval commitment batches or supplemental changes will depend on the cumulative stability data on developmental batches, primary batches, and/or production batches, as appropriate.

Table 6 illustrates the range of situations under which matrixing design is applicable, applicable if justified, generally not applicable, and not applicable. The table is intended, in a qualitative manner, to serve as a general guide for sponsors when determining if matrixing design is appropriate for a drug product with respect to the likelihood that such a design would result in a successful prediction of the expiration dating period. It does not seek to quantitatively define the different degrees of product stability or data variability.

Table 6: Applicability of Matrixing Design

Data Variability[b]	Product Stability[a]		
	Excellent	Moderate	Poor
Very Small	Applicable	Applicable	Applicable if justified
Moderate	Applicable	Applicable if justified	Generally not applicable
Large	Applicable if justified	Generally not applicable	Not Applicable

[a] In general, *moderate* and *excellent* stability mean little or no change in product test results for a period of 2-3 years and 4-5 years, respectively, as indicated by supportive data. *Poor stability* means measurable changes in test results within 1 year.

[b] Variability in supportive stability data within a given factor or across different factors.

d. Types of submission

Same as Section VII.G.1.c.

3. Design

a. General

For original applications, a matrixing design should always include the initial and final time points, as well as at least two additional time points through the first 12 months, that is at least three time points including the initial and 12-month time points. This approach is especially important if the original application contains less than full long-term data at the time of submission.

Although matrixing should not be performed across attributes, different matrixing designs for different attributes may be suitable where different testing frequencies can be justified. Likewise, each storage condition should be treated separately under its own matrixing design, if applicable. Care must be taken to ensure that there are at least three time points, including initial and end points, for each combination of factors under an accelerated condition. If bracketing is justified, the matrixing design should be developed afterward.

All samples should be placed on stability including those that are not to be tested under the matrixing design. Once the study begins, the protocol should be followed without deviation. The only exception is that, if necessary, it is acceptable to revert back to full stability testing during the study. But once reverted, the full testing should be carried out through expiry.

b. Size of matrixing design

The appropriate size of a matrix is generally related to the number of combinations of factors and the amount of supportive data available (Table 7). The size of a matrixing design is expressed as a fraction of the total number of samples to be tested in the corresponding full stability protocol. For a product available in 3 batches, 3 strengths, and 3 container/fill sizes, the number of combinations of factors to be tested in a full design is 3x3x3 or 27. Similarly, if there are 3 batches with one strength and no other factors, the number of combinations of factors is expressed as 3x1. The larger the number of combinations of factors to be tested *and* the greater the amount of available supportive data, the smaller the size of matrixing design that may be justified. The phrase *substantial amount of supportive data* means that a sufficient length of stability data are available on a considerable number of clinical/development batches, primary stability batches, and/or production batches to justify the use of matrixing design on primary stability batches, commitment batches, and/or annual batches and batches for postapproval changes. The formulations used in a matrixing design should be identical or very closely related, and the container/closure system should be the same between the supportive batches and the batches for which the matrixing design is intended. The size of matrixing design shown in the table takes into account all possible combinations of factors and time points. For example, where there are 3x3x3 combinations of factors and a substantial amount of supportive data are available, the size of the matrixing design could be as small as one half of that of a full testing protocol. Thus, *fractional* ½ means that only one half of the total number of samples in the corresponding full protocol will be tested under the matrixing design. Refer to Examples 2 and 3 below for two designs with an overall size of 5/12 and ½, respectively.

Table 7: Size of Matrixing Design[a]

Number of Combinations of Factors[a]	Amount of Supportive Data[c] Available		
	Substantial	Moderate	Little or none
Large (e.g., 3x3x3 or greater)	Fractional (e.g., ½)	Fractional (e.g., 5/8)	Full (i.e., no matrixing[d])
Moderate (e.g., 3x2)	Fractional (e.g., 5/8)	Fractional (e.g., 3/4)	Full (i.e., no matrixing)
Very small (e.g., 3x1)	Fractional (e.g., ¾)	Full (i.e., no matrixing)	Full (i.e., no matrixing)

[a] Expressed as a fraction of the total number of samples to be tested in the corresponding full design.

[b] Excluding time points.

[c] Cumulative stability data obtained from clinical/development batches, primary stability batches, and/or production batches, as appropriate, to form the basis to support the stability profile of the product.

[d] *No matrixing* means that matrixing is not suitable.

c. Statistical Considerations

The design should be well balanced. An estimate of the probability that stability outcomes from the matrixed study would be the same for a given factor or across different factors should be provided if available.[9]

d. Examples

Matrixing Example #1. Complete design with five-sevenths' time points (overall size: five-sevenths of full testing protocol)

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[9] For additional information on matrixing studies see W.R. Fairweather, T.-Y. D. Lin and R. Kelly, "Regulatory, Design, and Analysis Aspects of Complex Stability Studies," *J. Pharm. Sci.*, 84, 1322-1326, 1995.

The following example (Table 8) involves a complete design of 3x3x3 combinations of factors with five-sevenths' time points for a capsule dosage form available in 3 strengths of a common granulation and packaged in 3 container/closure systems and/or sizes: C1, HDPE bottle; 30 counts; C2, HDPE bottle, 100 counts; and blister-pack. A 24-month expiration dating period is proposed. While stability samples for all 27 combinations of factors will be tested, they will be tested only at five-sevenths of the usual time points; thus the overall size of design is 5/7 of the corresponding full testing protocol.

Table 8: Matrixing Example #1

Batch		1									2									3								
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure		C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Schedule		T1	T2	T3	T2	T3	T1	T3	T1	T2	T2	T3	T1	T3	T1	T2	T1	T2	T3	T3	T1	T2	T1	T2	T3	T2	T3	T1
Time Points (mo)	0	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	3	x					x		x				x		x		x				x		x					x
	6		x		x					x	x					x		x				x		x		x		
	9	x		x		x	x	x	x			x	x	x	x		x		x	x	x		x		x		x	x
	12		x	x	x	x		x		x	x	x		x		x		x	x	x		x		x	x	x	x	
	18	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	24	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Matrixing Example #2. Two-thirds fractional design with five-eighths time points (overall size: five-twelfths of full testing protocol)

The following example (Table 9) involves a two-thirds fractional design of 3x3x3 combinations of factors with five-eighths time points for a capsule dosage form which is available in 3 strengths of a common granulation and packaged in 3 container/closure systems and/or sizes: C1, HDPE bottle; 30 counts; C2, HDPE bottle, 100 counts; and C3, HDPE bottle, 200 counts. A 36-month expiration dating period is proposed. The overall size of this design can be referred to as 2/3 (of 27 combinations of factors) x 5/8 (of 8 time points), or 5/12 (of 216 samples in a full testing protocol).

Table 9: Matrixing Example #2

Batch		1									2									3								
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure		C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Schedule		T1	T2		T2		T1		T1	T2	T2		T1		T1	T2	T1	T2			T1	T2	T1	T2		T2		T1
Time Points (mo)	0	x	x		x		x		x	x	x		x		x	x	x	x			x	x	x	x		x		x
	3	x					x		x				x		x		x				x		x					x
	6		x		x					x	x					x		x				x		x		x		
	9	x					x		x				x		x		x				x		x					x
	12		x		x					x	x					x		x				x		x		x		
	18	x					x		x				x		x		x				x		x					x
	24		x		x					x	x					x		x				x		x		x		
	36	x	x		x		x		x	x	x		x		x	x	x	x			x	x	x	x		x		x

Matrixing Example #3. Bracketing design and three-fourths Matrix (overall size: one-half of full testing protocol)

The following example (Table 10) illustrates how bracketing (of one factor) and matrixing (with three-fourths time points) can be combined in one protocol. The description of the drug product is as shown in Example 2. The overall size of this design is 2/3 X 3/4, or ½ of that of a full testing protocol.

Table 10: Matrixing Example #3

Batch		1									2									3								
Strength		100 mg			200 mg			300 mg			100 mg			200 mg			300 mg			100 mg			200 mg			300 mg		
Container/ Closure		C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3	C1	C2	C3
Schedule		T1	T2	T3				T3	T1	T2	T2	T3	T1				T1	T2	T3	T3	T1	T2				T2	T3	T1
Time Points (mo)	0	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	3	x	x						x	x	x		x				x	x			x	x				x		x
	6		x	x				x		x	x	x						x	x	x		x				x	x	
	9	x		x				x	x			x	x				x		x	x	x						x	x
	12	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x
	18	x							x				x				x				x							x
	24		x	x				x		x	x	x						x	x	x		x				x	x	
	36	x	x	x				x	x	x	x	x	x				x	x	x	x	x	x				x	x	x

4. Data Evaluation

The stability data obtained under a matrixing protocol should be subjected to the same type of statistical analysis with the same vigor and for the same aspects as outlined in Section VII.E. The same principle and procedure on poolability (i.e., testing data from different batches for similarity before combining them into one overall estimate, as described in Section VII.E.1) should be applied.

I. Site-Specific Stability Data For Drug and Biologic Applications

1. Purpose

At the time of NDA submission, at least 12 months of long-term data and 6 months of accelerated data should be available on three batches of the drug substance (all of which should be at least pilot scale) and three batches of the drug product (two of which should be at least pilot scale); reference is made to the drug substance and drug product sections of the ICH Q1A Guidance and to Sections II.A and II.B. of this guidance, respectively. Because the ICH Guidance did not address where the stability batches should be made, this section provides recommendations on site-specific stability data: the number and size of drug substance and drug product stability batches made at the intended manufacturing-scale production sites and the length of stability data on these batches, for an original NDA, ANDA, BLA or PLA application. Applicants are advised to consult with the respective chemistry review team when questions arise.

2. Original NDAs, BLAs, or PLAs

In principle, primary stability batches should be made at the intended commercial site. If the primary stability batches are not made at the intended commercial site, stability data from the drug substance/product batches manufactured at that site (i.e., site-specific batches) should be included in the original submission to demonstrate that the product made at each site is equivalent. If at the time of application submission, there are 12 months of long-term data and 6 months of accelerated data on three primary stability batches made at other than the intended commercial site, a reduced number of site-specific batches with shorter duration of data than the primary batches may be acceptable. In addition, these site-specific batches may be of pilot scale.

A drug substance should be adequately characterized (i.e., results of chemical, physical, and, when applicable, biological testing). Material produced at different sites should be of comparable quality. In general, three to six months of stability data on one to three site-specific drug substance batches, depending on the availability of sufficient primary stability data from another site, should be provided at the time of application submission. Table 11 depicts the site-specific stability data recommended for the drug substance in an original application.

Table 11: Site-Specific Stability Data for a Drug Substance in an Original Application

Scenario[a]	Site-Specific Stability Data Recommended at Time of Submission[b]	Stability Commitment[c]
Sufficient primary stability data are available for the drug substance	3 months of accelerated (from a 6-month study) and long-term data on 1 site-specific batch.	First 3 drug substance production batches on long-term and accelerated stability studies.
Sufficient primary stability data are not available for the drug substance	3 months of accelerated (from a 6-month study) and long-term data on 3 site-specific batches.	First 3 drug substance production batches on long-term and accelerated stability studies.

[a] The phrase *sufficient primary stability data* means that, at the time of submission, there are 6 months of accelerated data and at least 12 months of long-term data on three primary stability batches made at a different pilot or production site from the intended site.

[b] Additional long-term stability data and, if applicable, accelerated data, should be submitted for review as soon as they become available prior to the approval.

[c] A commitment should be provided in the application to place the first three production batches at each site on long-term and accelerated stability studies and annual batches thereafter on long-term studies using the approved protocol and to report the resulting data in annual reports.

The complexity of the drug product dosage form is a critical factor in determining the number of site-specific batches for an original application. The quality and/or stability of a simple dosage form is less likely to vary due to a different manufacturing site than that of a complex dosage form. Three site-specific batches are needed for a complex dosage form to provide an independent and statistically meaningful stability profile for the product made at that site. One site-specific batch may be sufficient to verify the stability profile of a simple dosage form. Table 12, below, illustrates the site-specific stability data recommended for drug products in an original application:

Table 12: Site-Specific Stability Data for a Drug Product in an Original NDA, BLA, or PLA

Scenario[a]	Site-Specific Stability Data Recommended at Time of Submission[b]	Stability Commitment[c]
Simple dosage form where sufficient primary stability data are available	3 months of accelerated (from a 6-month study) and long-term data on 1 site-specific batch.	First 3 production batches on long-term and accelerated stability studies.
Complex dosage form where sufficient primary stability data are available	3 months of accelerated (from a 6-month study) and long-term data on 3 site-specific batches.	First 3 production batches on long-term and accelerated stability studies.
Any dosage form where sufficient primary stability data are not available	6 months of accelerated and 12 months of long-term data on 3 site-specific batches.	First 3 production batches on long-term and accelerated stability studies.

[a] The phrase *sufficient primary stability data* means that, at the time of submission, there are 6 months of accelerated data and at least 12 months of long-term data on three primary stability batches made at a different pilot or production site from the intended site.

[b] Additional long-term stability data and, if applicable, accelerated data should be submitted for review as soon as they become available prior to the approval.

[c] A commitment should be provided in the application to place the first 3 production batches at each site on long-term and accelerated stability studies and annual batches thereafter on long-term studies using the approved protocol and to report the resulting data in annual reports.

Other factors, such as lack of experience at the new site in a particular dosage form, or difference in the environmental conditions between the sites, can potentially affect the quality and/or stability of a drug product. Therefore, one site-specific batch may not be sufficient in these cases. More than one site-specific batch may be needed for a drug substance/product that is intrinsically unstable.

Although one site-specific batch may be sufficient under certain situations, the data so generated, particularly if limited to accelerated studies, may not be amenable to statistical analysis for the establishment of a retest period or expiration dating period. Instead, the single site-specific batch may only serve to verify the stability profile of a drug substance/product that has been established based on primary stability batches at a pilot plant.

In general, site-specific drug product batches should be made with identifiable site-specific drug substance batches both for original applications, wherever possible, and for postapproval stability commitment.

Although pilot and commercial facilities may or may not be located on the same campus or within the same geographical area, they will generally employ similar processes and equipment of the same design and operating principles. If different processes and/or equipment are used, more site-specific batches and/or longer duration of data are recommended. If the pilot plant where the primary stability batches are made is located at the intended commercial site (i.e., on the same campus as the intended manufacturing-scale production facility) the site-specific stability recommendations are met (provided the processes and equipment are the same) and no additional data will be needed. A commitment should be made to place the first three production batches on accelerated and long-term stability studies. If more than one manufacturing-scale production site is proposed for an original NDA, BLA or PLA, the recommendations above would be applicable to each site.

3. Site-Specific Data Package Recommendations for ANDAs

For ANDAs, the primary batch(es) to support the application are usually manufactured in the production facility. If the primary stability batch(es) are not made at the intended commercial site, stability data should be generated, as outlined in Table 13, on the drug product manufactured at that site, i.e. site-specific batches, and the data should be included in the original submission to demonstrate that the product made at each site is equivalent.

If the pilot plant where the primary stability batches are made is located at the intended commercial site (i.e., on the same campus as the intended commercial facility), the site-specific stability recommendations are met and no additional data will be needed. A commitment should be made to place the first three production batches and annual batches thereafter on long-term stability studies.

For complex dosage forms as described in the previous section, a reduced number of site-specific batches may be justified if accelerated and long-term data are available at the time of application submission on batches made at a different pilot or commercial site from the intended commercial facility.

Table 13: Site-Specific Stability Data for a Drug Product in an Original ANDA

Scenario	Site-Specific Stability Data Recommended at Time of Submission[a]	Stability Commitment[b]
Simple Dosage Form	3 months of accelerated and available long-term data on 1 site-specific batch.	First 3 production batches on long-term stability studies.
Complex Dosage Form	3 months of accelerated and available long-term data on 3 site-specific batches.	First 3 production batches on long-term stability studies.

[a] Drug substance batches used to produce site-specific drug product batches should be clearly identified. Additional long-term stability data should be submitted for review as soon as they become available prior to approval.

[b] A commitment should be provided in the application to place the first three production batches at each site on long-term stability studies and annual batches thereafter on long-term studies using the approved protocol and to report the resulting data in annual reports.

J. Photostability

1. General

The ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the *parent guidance*) notes that light testing should be an integral part of stress testing.

The ICH Q1B guidance *Photostability Testing of New Drug Substances and Products* primarily addresses the generation of photostability information for new molecular entities and associated drug products and the use of the data in determining whether precautionary measures in manufacturing, labeling, or packaging are needed to mitigate exposure to light. Q1B does not specifically address other photostability studies that may be needed to support, for example, the photostability of a product under in-use conditions or the photostability of analytical samples. Because data are generated on a directly exposed drug substance alone and/or in simple solutions and drug products when studies are conducted as described in the Q1B guidance, knowledge of photostability characteristics may be useful in determining when additional studies may be needed or in providing justification for not performing additional studies. For example, if a product has been determined to photodegrade upon direct exposure but is adequately protected by packaging, an in-use study may be needed to support the use of the product (e.g., a parenteral drug that is infused over a period of time). The test conditions for in-use studies will vary depending on the product and use but should depend on and relate to the directions for use of the particular product.

Photostability studies are usually conducted only in conjunction with the first approval of a new molecular entity. Under some circumstances, photostability studies should be repeated if certain postapproval or supplemental changes, such as changes in formulation or packaging, are made to the product, or if a new dosage form is proposed. Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of changes made. For example, if initial studies demonstrate that an active moiety in a simple solution degrades upon exposure to light and the tablet drug product is stable, a subsequent filing requesting approval of a liquid dosage form may warrant additional studies to characterize the photostability characteristics of the new dosage form.

Photostability studies need not be conducted for products that duplicate a commercially available listed drug product provided that the packaging (immediate container/closure and market pack) and labeling storage statements regarding light duplicate those of the reference listed drug. If deviations in packaging or labeling statements are made, additional studies may be recommended. The decision as to whether additional studies should be conducted will be made on a case-by-case basis by the chemistry review team.

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described in the section Selection of Batches, in the parent guidance. Under some circumstances, these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and/or change made. [ICH Q1B]

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

- Tests on the drug substance;
- Tests on the exposed drug product outside of the immediate pack; and if necessary,
- Tests on the drug product in the immediate pack; and if necessary,
- Tests on the drug product in the marketing pack.[ICH Q1B]

The extent of drug product testing should be established by assessing whether or not acceptable change has occurred at the end of the light exposure testing as described in Figure 2, the Decision Flow Chart for Photostability Testing of Drug Products. Acceptable change is change within limits justified by the applicant. [ICH Q1B]

The formal labeling requirements for photolabile drug substances and drug products are established by national/regional requirements. [ICH Q1B]

2. Light Sources

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer/applicant can rely on the spectral distribution specification of the light source manufacturer. [ICH Q1B]

Option 1

Any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nanometers (nm), an appropriate filter(s) may be fitted to eliminate such radiation. [ICHQ1B]

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near ultraviolet lamp.

- A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977 (1993); and

- A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm. [ICH Q1B]

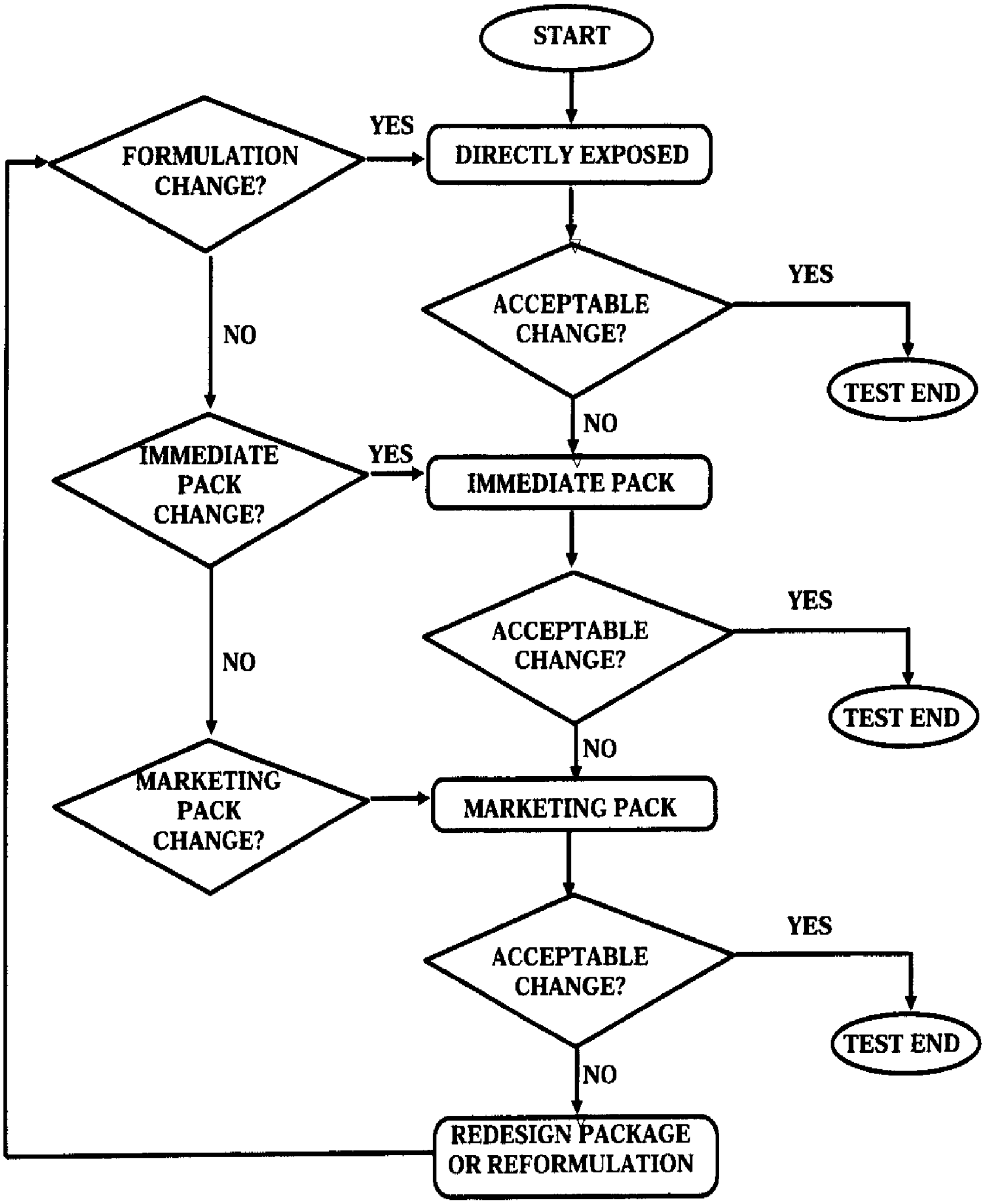
3. Procedure [ICH Q1B]

For confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter to allow direct comparisons to be made between the drug substance and drug product.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample. [ICH Q1B]

DECISION FLOW CHART FOR PHOTOSTABILITY TESTING OF DRUG PRODUCTS



4. Drug Substance [ICH Q1B]

For drug substances, photostability testing should consist of two parts: Forced degradation testing and confirmatory testing.

The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes, it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photostable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be examined further.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling (see Section VIII.J.3., Procedure, and 4.a., Presentation of Samples, for information on the design of these studies).

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the parent guidance.

a. Presentation of Samples [ICH Q1B]

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation, or melting are minimized. All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 millimeters. Drug substances that are liquids should be exposed in chemically inert and transparent containers.

b. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark control if these are used in the test.

c. Judgment of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies to ensure that the drug will be within justified limits at time of use (see the relevant ICH stability and impurity guidance).

5. Drug Product [ICH Q1B]

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in Section VII.J.3.

Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the parent guidance if the product is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products, such as infusion liquids or dermal creams, to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

a. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account, and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be chosen to provide minimal interference with the irradiation of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets and capsules should be spread in a single layer.

If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large volume containers (e.g., dispensing packs).

b. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution, dissolution/disintegration for dosage forms such as capsules) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

c. Judgment of Results

Depending on the extent of change, special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies to ensure that the product will be within proposed specifications during the shelf life (see the relevant ICH stability and impurity guidance).

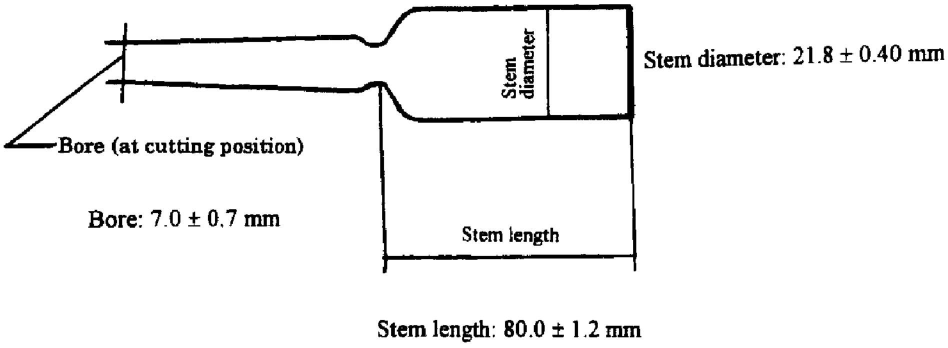
6. Quinine Chemical Actinometry [ICH Q1B]

The following provides details of an actinometric procedure for monitoring exposure to a near UV fluorescent lamp (based on work done by FDA/National Institute of Standards and Technology study). For other light sources/actinometric systems, the same approach may be used, but each actinometric system should be calibrated for the light source used.

Prepare a sufficient quantity of a 2 percent weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary, dissolve by heating).

Option 1

Put 10 milliliters (mL) of the solution into a 20 mL colorless ampoule (see drawing, below), seal it hermetically, and use this as the sample. Separately, put 10 mL of the solution into a 20 mL colorless ampoule (see note 1), seal it hermetically, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure, determine the absorbances of the sample (AT) and the control (AO) at 400 nm using a 1 centimeter (cm) path length. Calculate the change in absorbance units (AU): A = AT - AO. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.9 AU. *Note: Shape and Dimensions (See Japanese Industry Standard (JIS) R3512 (1974) for ampoule specifications).*[10]


Stem diameter
Stem diameter: 21.8 ± 0.40 mm
Bore (at cutting position)
Bore: 7.0 ± 0.7 mm
Stem length
Stem length: 80.0 ± 1.2 mm

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[10] Yoshioka, S., "Quinine Actinometry as a Method for Calibrating Ultraviolet Radiation Intensity in Light-stability Testing of Pharmaceuticals," *Drug Development and Industrial Pharmacy*, 20(13):2049-2062, 1994

Option 2

Fill a 1 cm quartz cell and use this as the sample. Separately fill a 1 cm quartz cell, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure, determine the absorbances of the sample (AT) and the control (AO) at 400 nm. Calculate the change in absorbance,) A = AT - AO. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.5.

Alternative packaging configurations may be used if appropriately validated. Alternative validated chemical actinometers may be used.

7. Acceptable/Unacceptable Photostability Change

The extent of the drug product photostability testing depends on the change that has occurred at the end of each test tier described in Figure 2, above, the Decision Flow Chart for Photostability Testing of Drug Products. Test results that are outside the proposed acceptance criteria for the product would not be considered acceptable change. This is a stress test designed to determine the intrinsic photostability characteristics of new drug substances and products, and no correlation has been developed to equate a within specification result to an expiration dating period. The acceptability of any observed changes should be justified in the application. It may be important to consider other degradative processes (e.g., thermal) when justifying a photostability change as acceptable because the processes may be independent and additive. For example, a 5 percent loss in potency due to photodegradation may be considered acceptable if that is the only type of degradation observed. If the product is also expected to degrade 5 percent over the shelf-life due to thermal degradation, the photodegradation may then be considered unacceptable based on the potential additive effect of the changes. In this case, precautions should be taken to mitigate the product’s exposure to light.

Under the intense light exposure conditions included in the Q1B guidance, certain colors in solid dosage forms may fade. Quantitative analysis of the color change is not recommended as these changes are not likely to occur under actual storage conditions. In the absence of change in other parameters such as assay, these color changes may be acceptable.

8. Photostability Labeling Considerations

The data generated using the procedure described in the ICH Q1A guidance is useful in determining when special handling or storage statements regarding exposure to light should be included in the product labeling (21 CFR 201.57(k)(4)). The labeling guidance provided below pertains only to products as packaged for distribution. Instructions and stability statements that may be needed to address in-use conditions pursuant to 21 CFR 201.57(j) are not covered.

Change after direct exposure: If changes that are observed when the product is directly exposed under the light conditions described in the Q1B guidance are acceptable, no labeling storage statement regarding light is needed.

Change after exposure in the immediate container/closure: If changes observed when the product is directly exposed are unacceptable, but are acceptable when the product is tested in the immediate container/closure under the conditions described in the Q1B guidance, the inclusion of a labeling storage statement regarding light would depend on the likelihood of the product being removed from the immediate package during the distribution process.

- For those products that are unlikely to be removed from the immediate container, such as creams or ointments in tubes dispensed directly to the patient, and ophthalmic products, the use of a labeling storage statement regarding light is optional.

- For products that may be removed from the immediate pack, such as pharmacy bulk packs, a light storage statement should be included such as “PROTECT FROM LIGHT. Dispense in a light-resistant container.”

Change after exposure in the market pack: If changes that are observed are acceptable only when the product in the market pack is exposed under the conditions described in the Q1B guidance, labeling storage statements regarding light should be included.

Examples of typical storage statements are, for single-dose and multiple-dose products respectively, “PROTECT FROM LIGHT. Retain in carton until time of use.” and “PROTECT FROM LIGHT. Retain in carton until contents are used.”

K. Degradation Products

When degradation products are detected upon storage, the following information about them should be submitted:

- Procedure for isolation and purification
- Identity and chemical structures
- Degradation pathways
- Physical and chemical properties
- Detection and quantitation levels
- Acceptance Criteria (individual and total)
- Test methods
- Validation data
- Biological effect and pharmacological actions, including toxicity studies, at the concentrations likely to be encountered (cross-reference to any available information is acceptable)

If racemization of the drug substance in the dosage form is possible, the information described above also should be provided.

L. Thermal Cycling

A study of the effects of temperature variation, particularly if appropriate for the shipping and storage conditions of certain drug products, should be considered. Drug products susceptible to phase separation, loss of viscosity, precipitation, and aggregation should be evaluated under such thermal conditions. As part of the stress testing, the packaged drug product should be cycled through temperature conditions that simulate the changes likely to be encountered once the drug product is in distribution.

- A temperature cycling study for drug products that may be exposed to temperature variations above freezing may consist of three cycles of two days at refrigerated temperature (2-8°C) followed by two days under accelerated storage conditions (40°C).

- A temperature cycling study for drug products that may be exposed to sub-freezing temperatures may consist of three cycles of two days at freezer temperature (-10° to -20°C) followed by two days under accelerated storage conditions (40°C).

- For inhalation aerosols, the recommended cycle study consists of three or four six-hour cycles per day, between subfreezing temperature and 40°C (75-85 percent RH) for a period of up to six weeks.

- For frozen drug products, the recommended cycle study should include an evaluation of effects due to accelerated thawing in a microwave or a hot water bath unless contraindicated in the labeling.

- Alternatives to these conditions may be acceptable with appropriate justification.

M. Stability Testing in Foreign Laboratory Facilities

Stability testing (as well as finished product release testing) performed in any foreign or domestic facility may be used as the basis for approval of an application. This includes all NDAs, ANDAs, and related CMC supplements. A satisfactory inspection of the laboratory(ies) that will perform the testing will be necessary.[11]

Applicants should consider the effects of bulk packaging, shipping, and holding of dosage forms and subsequent market packaging, and distribution of the finished drug product, and be aware of the effect of such operations on product quality. Time frames should be established to encompass the date of production, date of quality control release of the dosage form, bulk packaging, shipping, and market packaging, and initiation and performance of the stability studies on the drug product should be established, controlled, and strictly followed. Maximum time frames for each operation should be established and substantiated by the applicant.

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[11] This statement replaces a previous position, established via a CDER Office of Generic Drugs guidance, which recommended that finished product and stability testing be conducted at a United States laboratory for drug products manufactured in foreign facilities and shipped in bulk containers to the United States for packaging into immediate containers for marketing.

N. Stability Testing of Biotechnology Drug Products

1. General [ICH Q5C]

The ICH harmonized tripartite guidance entitled Q1A *Stability Testing of New Drug Substances and Products* issued by ICH on October 27, 1993, applies in general to biotechnological/biological products. However, biotechnological/biological products have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence, of biological activity, is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. To ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With these concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions that can affect the product’s potency, purity, and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

2. Scope [ICH Q5C]

The guidance in this section applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components and which are isolated from tissues, body fluids, cell cultures, or produced using recombinant deoxyribonucleic acid (r-DNA) technology. Thus, the section covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the product review office. The section does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

3. Terminology [ICH Q5C]

For the basic terms used in this section, the reader is referred to the Glossary. However, because manufacturers of biotechnological/biological products sometimes use traditional terminology, traditional terms are specified in parentheses to assist the reader.

4. Selection of Batches [ICH Q5C]

a. Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture, but before formulation and final manufacturing, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of six months' stability data at the time of submission should be submitted in cases where storage periods greater than six months are requested. For drug substances with storage periods of less than six months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot-scale batches of drug substance produced at a reduced scale of fermentation and purification may be provided at the time the application is submitted to the Agency with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval.

The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the drug substance (bulk material) made at pilot-scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale. The drug substance entered into the stability program should be stored in containers that properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for drug substance stability testing provided that they are constructed of the same material and use the same type of container/closure system that is intended to be used during manufacture.

b. Intermediates

During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that ensure their stability within the bounds of the developed process. Although the use of pilot-scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing-scale process.

c. Drug Product (Final Container Product)

Stability information should be provided on at least three batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of six months' data at the time of submission should be submitted in cases where storage periods greater than six months are requested. For drug products with storage periods of less than six months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Product expiration dating should be based upon the actual data submitted in support of the application. Because dating is based upon the real-time/real-temperature data submitted for review, continuing updates of initial stability data should occur during the review and evaluation process. The quality of the final container product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies. Data from pilot-scale batches of drug product may be provided at the time the application is submitted to the Agency with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval. Where pilot-plant scale batches were submitted to establish the dating for a product and, in the event that the product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating period or is not representative of the material used in preclinical and clinical studies, the applicant should notify the appropriate FDA reviewing office to determine a suitable course of action.

d. Sample Selection

Where one product is distributed in batches differing in fill volume (e.g., 1 milliliter (mL), 2 mL, or 10 mL), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 milligram (mg), 2 mg, or 5 mg), samples to be entered into the stability program may be selected on the basis of a matrix system and/or by bracketing.

Matrixing — the statistical design of a stability study in which different fractions of samples are tested at different sampling points — should only be applied when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same closure, and, possibly, in some cases, different container/closure systems. Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers/closures, where it cannot be confirmed that the products respond similarly under storage conditions,

Where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program (i.e., bracketing). The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples are represented by those at the extremes. In certain cases, data may be needed to demonstrate that all samples are properly represented by data collected for the extremes.

5. Stability-Indicating Profile [ICH Q5C]

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-indicating profile, and the data should be available for review. The determination of which tests should be included will be product-specific. The items emphasized in the following subsections are not intended to be all-inclusive, but represent product characteristics that should typically be documented to demonstrate product stability adequately.

a. Protocol

The marketing application should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods. The protocol should include all necessary information that demonstrates the stability of the biotechnological/biological product throughout the proposed expiration dating period including, for example, well-defined specifications and test intervals. The statistical methods that should be used are described in the ICH Q1A guidance on stability.

b. Potency

When the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. For the purpose of stability testing of the products described in this guidance, potency is the specific ability or capacity of a product to achieve its intended effect. It is based on the measurement of some attribute of the product and is determined by a suitable in vivo or in vitro quantitative method. In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an appropriate reference material. For that purpose, a reference material calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay.

Potency studies should be performed at appropriate intervals as defined in the stability protocol and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standards. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material.

In some biotechnological/biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active ingredient(s) from the carrier used in conjugates or adjuvants should be examined in real-time/real-temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be difficult because, in some cases, in vitro tests for biological activity and physicochemical characterization are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product before conjugation/binding, assessing the release of the active compound from the second moiety, in vivo assays) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

c. Purity and Molecular Characterization

For the purpose of stability testing of the products described in this guidance, purity is a relative term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological/biological product is extremely difficult to determine. Thus, the purity of a biotechnological/biological product should be typically assessed by more than one method and the purity value derived is method-dependent. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.

The degree of purity, as well as the individual and total amounts of degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterization of the drug substance and/or drug product (e.g., molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g., reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

d. Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/biological products should be monitored and reported for the drug product in its final container:

- Visual appearance of the product (color and opacity for solutions/suspensions; color, texture, and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.

- Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf life.

- Additives (e.g., stabilizers, preservatives) or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely affect the quality of the drug product, these items may need to be monitored during the stability program.

- The container/closure has the potential to affect the product adversely and should be carefully evaluated (see below).

6. Storage Conditions [ICH Q5C]

a. Temperature

Because most finished biotechnological/biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

b. Humidity

Biotechnological/biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

c. Accelerated and Stress Conditions

As previously noted, the expiration dating should be based on real-time/real-temperature data. However, it is strongly recommended that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information or future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information that may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. Although the OCH Q1A guidance on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.

d. Light

Applicants should consult the FDA on a case-by-case basis to determine guidance for testing.

e. Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/biological product and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure) as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container/closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, packages, and/or package inserts. Such labeling should be in accordance with FDA requirements.

f. Stability after Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labeling should be in accordance with FDA requirements.

7. Testing Frequency [ICH Q5C]

The shelf lives of biotechnological/biological products may vary from days to several years. Thus, it is difficult to draft uniform guidances regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological/biological products. With only a few exceptions, however, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf lives in that range. This takes into account the fact that degradation of biotechnological/biological products may not be governed by the same factors during different intervals of a long storage period.

When shelf lives of one year or less are proposed, the real-time stability studies should be conducted monthly for the first three months and at three month intervals thereafter. For products with proposed shelf lives of greater than one year, the studies should be conducted every three months during the first year of storage, every six months during the second year, and annually thereafter.

While the testing intervals listed above may be appropriate in the preapproval or prelicense stage, reduced testing may be appropriate after approval or licensing where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol that supports elimination of specific test intervals (e.g., nine-month testing) for postapproval/postlicensing, long-term studies.

8. Specifications [ICH Q5C]

Although biotechnological/biological products may be subject to significant losses of activity, physicochemical changes, or degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end of shelf life specifications. Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during the proposed shelf life have not been developed for individual types or groups of biotechnological/biological products but are considered on a case-by-case basis. Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf life. These specifications and limits should be derived from all available information using the appropriate statistical methods. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that the clinical performance is not affected, as discussed in the OCH Q1A guidance on stability.

9. Labeling [ICH Q5C]

For most biotechnological/biological drug substances and drug products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for drug substances and drug products that cannot tolerate freezing. These conditions, and where appropriate, recommendations for protection against light and/or humidity, should appear on containers, packages, and/or package inserts. Such labeling should be in accordance with section II.B.11 of this document.

VIII. CONSIDERATIONS FOR SPECIFIC DOSAGE FORMS

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. In general, appearance, assay, and degradation products should be evaluated for all dosage forms.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular drug product (for example, a test for odor should be performed only when necessary and with consideration for analyst safety). Furthermore, it is not expected that every listed test be performed at each time point.

A. Tablets

Tablets should be evaluated for appearance, color, odor, assay, degradation products, dissolution, moisture, and friability.

B. Capsules

Hard gelatin capsules should be evaluated for appearance (including brittleness), color, odor of contents, assay, degradation products, dissolution, moisture, and microbial limits.

Testing of soft gelatin capsules should include appearance, color, odor of content, assay, degradation products, dissolution, microbial limits, pH, leakage, and pellicle formation. In addition, the fill medium should be examined for precipitation and cloudiness.

C. Emulsions

An evaluation should include appearance (including phase separation), color, odor, assay, degradation products, pH, viscosity, microbial limits, preservative content, and mean size and distribution of dispersed phase globules.

D. Oral Solutions and Suspensions

The evaluation should include appearance (including formation of precipitate, clarity for solutions), color, odor, assay, degradation products, pH, preservative content, and microbial limits.

Additionally, for suspensions, redispersibility, rheological properties, and mean size and distribution of particles should be considered. After storage, samples of suspensions should be prepared for assay according to the recommended labeling (e.g., shake well before using).

E. Oral Powders for Reconstitution

Oral powders should be evaluated for appearance, odor, color, moisture, and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described in VIII.D. above, after preparation according to the recommended labeling, through the maximum intended use period.

F. Metered-Dose Inhalations and Nasal Aerosols

Metered-dose inhalations and nasal aerosols should be evaluated for appearance (including content, container, valve and its components), color, taste, assay, degradation products, assay for co-solvent (if applicable), dose content uniformity, labeled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, microbial limits, valve delivery (shot weight), and extractables/leachables from plastic and elastomeric components. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, the appearance of the valve components and container’s contents should be evaluated microscopically for large particles and changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, as well as foreign particulate matter. These particles lead to clogged valves or non-reproducible delivery of a dose. Corrosion of the inside of the container or deterioration of the gaskets may adversely affect the performance of the drug product.

A stress temperature cycling study should be performed under the extremes of high and low temperatures expected to be encountered during shipping and handling to evaluate the effects of temperature changes on the quality and performance of the drug product. Such a study may consist of three or four six-hour cycles per day, between subfreezing temperature and 40°C (75-85 percent RH), for a period of up to six weeks.

Because the inhalant drug products are intended for use in the respiratory system, confirmation that initial release specifications are maintained should be provided to ensure the absence of pathogenic organisms (e.g., Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Salmonella species) and that the total aerobic count and total mold and yeast count per canister are not exceeded.

G. Inhalation Solutions and Powders

The evaluation of inhalation solutions and solutions for inhalation should include appearance, color, assay, degradation products, pH, sterility, particulate matter, preservative and antioxidant content (if present), net contents (fill weight/volume), weight loss, and extractables/leachables from plastic, elastomeric and other packaging components.

The evaluation of inhalation powders should include appearance, color, assay, degradation products, aerodynamic particle size distribution of the emitted dose, microscopic evaluation, microbial limit, moisture content, foreign particulates, content uniformity of the emitted dose, and number of medication doses per device meeting content uniformity of the emitted dose (device metered products).

H. Nasal Sprays: Solutions and Suspensions

The stability evaluation of nasal solutions and suspensions equipped with a metering pump should include appearance, color, clarity, assay, degradation products, preservative and antioxidant content, microbial limits, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter, and extractables/leachables from plastic and elastomeric components of the container, closure, and pump.

I. Topical, Ophthalmic and Otic Preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, and nonmetered aerosols for application to the skin.

Topical preparations should be evaluated for appearance, clarity, color, homogeneity, odor, pH, resuspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), assay, degradation products, preservative and antioxidant content (if present), microbial limits/sterility, and weight loss (when appropriate).

Appropriate stability data should be provided for products supplied in closed-end tubes to support the maximum anticipated use period, during patient use, once the tube seal is punctured allowing product contact with the cap/cap liner. Ointments, pastes, gels, and creams in large containers, including tubes, should be assayed by sampling at the surface, top, middle, and bottom of the container. In addition, tubes should be sampled near the crimp (see also Section VII.D.2.).

Evaluation of ophthalmic or otic products (e.g., creams, ointments, solutions, and suspensions) should include the following additional attributes: sterility, particulate matter, and extractables.

Evaluation of nonmetered topical aerosols should include: appearance, assay, degradation products, pressure, weight loss, net weight dispensed, delivery rate, microbial limits, spray pattern, water content, and particle size distribution (for suspensions).

J. Transdermals

Stability studies for devices applied directly to the skin for the purpose of continuously infusing a drug substance into the dermis through the epidermis should be examined for appearance, assay, degradation products, leakage, microbial limit/sterility, peel and adhesive forces, and the drug release rate.

K. Suppositories

Suppositories should be evaluated for appearance, color, assay, degradation products, particle size, softening range, appearance, dissolution (at 37°C,) and microbial limits.

L. Small Volume Parenterals (SVPs)

SVPs include a wide range of injection products such as *Drug Injection*, *Drug for Injection*, *Drug Injectable Suspension*, *Drug for Injectable Suspension*, and *Drug Injectable Emulsion*.

Evaluation of *Drug Injection* products should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, and pyrogenicity.

Stability studies for *Drug for Injection* products should include monitoring for appearance, clarity, color, reconstitution time, and residual moisture content. The stability of *Drug for Injection* products should also be evaluated after reconstitution according to the recommended labeling. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labeling, should include appearance, clarity, odor, color, pH, assay (potency), preservative (if present), degradation products/aggregates, sterility, pyrogenicity, and particulate matter.

The stability studies for *Drug Injectable Suspension* and *Drug for Injectable Suspension* products should also include particle size distribution, redispersibility, and rheological properties in addition to the parameters cited above for *Drug Injection* and *Drug for Injection* products.

The stability studies for *Drug Injectable Emulsion* products should include, in addition to the parameters cited above for *Drug Injection*, phase separation, viscosity, and mean size and distribution of dispersed phase globules.

The functionality and integrity of parenterals in prefilled syringe delivery systems should be ensured through the expiration dating period with regard to factors, such as the applied extrusion force, syringeability, pressure rating, and leakage.

Continued assurance of sterility for all sterile products can be assessed by a variety of means, including evaluation of the container and closure integrity by appropriate challenge test(s), and/or sterility testing as described in Section VII.C. Stability studies should evaluate product stability following exposure to at least the maximum specified process lethality (e.g., F_0, Mrads).

Inclusion of testing for extractables/leachables in the stability protocol may be appropriate in situations where other qualification tests have not provided sufficient information or assurance concerning the levels of extractables/leachables from plastics and elastomeric components.

Interaction of administration sets and dispensing devices with parenteral drug products, where warranted, should also be considered through appropriate use test protocols to assure that absorption and adsorption during dwell time do not occur.

M. Large Volume Parenterals (LVPs)

Evaluation of LVPs should include appearance, color, assay, preservative content (if present), degradation products, particulate matter, pH, sterility, pyrogenicity, clarity, and volume.

Continued assurance of sterility for all sterile products may be assessed by a variety of means, including evaluation of the container and closure integrity by appropriate challenge test(s) and/or sterility testing as described in Section VII.C. Stability studies should include evaluation of product stability following exposure to at least the maximum specified process lethality (e.g., F_0, Mrads).

Interaction of administration sets and dispensing devices with this type of dosage form should also be considered through appropriate use test protocols to ensure that absorption and adsorption during dwell time do not occur.

N. Drug Additives

For any drug product or diluent that is intended for use as an additive to another drug product, the potential for incompatibility exists. In such cases, the drug product labeled to be administered by addition to another drug product (e.g., parenterals, inhalation solutions), should be evaluated for stability and compatibility in admixture with the other drug products or with diluents both in upright and inverted/on-the-side orientations, if warranted.

A stability protocol should provide for appropriate tests to be conducted at 0-, 6-to-8-, and 24-hour time points, or as appropriate over the intended use period at the recommended storage/use temperature(s). Tests should include appearance, color, clarity, assay, degradation products, pH, particulate matter, interaction with the container/closure/device, and sterility. Appropriate supporting data may be provided in lieu of an evaluation of photodegradation.

The compatibility and the stability of the drug products should be confirmed in all diluents and containers and closures as well as in the presence of all other drug products indicated for admixture in the labeling. Compatibility studies should be conducted on at least the lowest and highest concentrations of the drug product in each diluent as specified in the labeling. The stability and compatibility studies should be performed on at least three batches of the drug product. Compatibility studies should be repeated if the drug product or any of the recommended diluents or other drug products for admixture are reformulated.

Testing for extractables/leachables on stability studies may be appropriate in situations where other qualification tests have not provided sufficient information or assurance concerning the levels of extractables/leachables from plastics and elastomeric components. Interaction of administration sets and dispensing devices with parenteral drug products, where warranted, should also be considered through appropriate use test protocols to ensure that absorption and adsorption during dwell time do not occur.

O. Implantable Subdermal, Vaginal and Intrauterine Devices that Deliver Drug Products

A device containing a drug substance reservoir or matrix from which drug substance diffuses should be tested for total drug substance content, degradation products, extractables, in vitro drug release rate, and as appropriate, microbial burden or sterility. The stability protocol should include studies at 37°C or 40°C over a sufficient period of time to simulate the in vivo use of the drug delivery device.

Stability testing for intrauterine devices (IUDs) 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.

IX. STABILITY TESTING FOR POSTAPPROVAL CHANGES

A. General

Due to the great variety of changes that may be encountered after a drug application is approved, it is impossible to address stability requirements for all changes in an exhaustive manner in this guidance. Some more common examples of changes to an approved drug application for which supportive stability data should be submitted are listed below. All changes should be accompanied by the standard stability commitment to conduct and/or complete long-term stability studies on the first 1 or 3 batches of the drug substance and/or drug product and annual batches thereafter, in accordance with the approved stability protocol. The accumulated stability data should be submitted in the subsequent annual reports. Unless otherwise noted, if the data give no reason to believe that the proposed change will alter the stability of the drug product, the previously approved expiration dating period can be used.

Historically, all postapproval changes were considered together and required extensive stability documentation. With the publication of the SUPAC-IR guidance, this approach was changed and the likelihood of a specific CMC change affecting a drug product's performance was considered in creating a multitiered system for evaluating postapproval changes. That system is used in this guidance. With a higher level change, more stability data will be expected to support that change. Thus, five stability data package types have been defined, as explained in Table 14.

Table 14: Stability Data Packages to Support Postapproval Changes

Stability Data Package	Stability Data at Time of Submission	Stability Commitment
Type 0	None	None beyond the regular annual batches
Type 1	None	First (1) production batch and annual batches thereafter on long-term stability studies.
Type 2	3 months of comparative accelerated data and available long-term data on 1 batch[a] of drug product with the proposed change.	First (1) production batch[b] and annual batches thereafter on long-term stability studies[c].
Type 3	3 months of comparative accelerated data and available long-term data on 1 batch[a] of drug product with the proposed change.	First 3 production batches[b] and annual batches thereafter on long-term stability studies.[c]
Type 4	3 months of comparative accelerated data and available long-term data on 3 batches[a] of drug product with the proposed change.	First 3 production batches[b] and annual batches thereafter on long-term stability studies.[c]

[a] Pilot scale batches acceptable.

[b] If not submitted in the supplement.

[c] Using the approved stability protocol and reporting data in annual reports.

The following sections address a number of possible postapproval changes and contain summary tables with examples of the different levels of change, the stability data package type and, wherever possible, the filing documentation (AR = annual report; CBE = changes-being-effected supplement; PA = prior approval supplement) recommended to support each change. The information presented here is not intended to be exhaustive. Where a specific issue is not covered, consultation with FDA staff is recommended.

B. Change in Manufacturing Process of the Drug Substance

A change in the manufacturing process of the drug substance at the approved manufacturing site should be supported by the submission of sufficient data to show that such a change does not compromise the quality, purity, or stability of the drug substance and the resulting drug product. Because chemical stability of a substance is an intrinsic property, changes made in the preparation of that substance should not affect its stability, provided the isolated substance remains of comparable quality for attributes such as particle size distribution, polymorphic form, impurity profile, and other physiochemical properties. Special concerns for biological products may exist if changes are made in the manufacturing process of a drug substance that may not exist in a chemically synthesized drug substance.

Specific submission and stability issues will be addressed in detail in a separate forthcoming guidance dealing with postapproval changes for drug substances.

C. Change in Manufacturing Site

Site changes consist of changes in the location of the site of manufacture, packaging operations, and/or analytical testing laboratory both of company-owned as well as contract manufacturing facilities. The stability data package and filing mechanisms indicated below apply to site changes only. If other changes occur concurrently, the most extensive data package associated with the individual changes should be submitted.

When a change to a new manufacturer or manufacturing site for any portion of the manufacturing process of a drug substance or drug product is made, sufficient data to show that such a change does not alter the characteristics or compromise the quality, purity, or stability of the drug substance or drug product may be necessary. The data should include a side-by-side comparison of all attributes to demonstrate comparability and equivalency of the drug substance or drug product manufactured at the two facilities. New manufacturing locations should have a satisfactory CGMP inspection.

1. Site Change for the Drug Substance

For a change limited to an alternate manufacturing site for the drug substance using similar equipment and manufacturing process, stability data on the drug substance may not always be necessary because, for essentially pure drug substances, stability is an intrinsic property of the material. Biotechnology and biologic products may be an exception (see 21 CFR 601.12 and 314.70 (g)). In general, such a change can be made in a CBE supplement as allowed under 21

CFR 314.70(c)(3). The standard stability commitment should be made to conduct long-term stability studies in accordance with the approved stability protocol on the first production batch of drug product produced from a production batch of drug substance manufactured at the new site. Ordinarily, the approved expiration dating period for the drug product may be retained if the drug substance is shown to be of comparable quality (e.g., particle size distribution, polymorphic form, impurity profile, and other physiochemical properties). If the drug substance is not of comparable quality, then more extensive stability data on the drug product manufactured from the drug substance will be needed.

Specific submission and stability issues pertaining to manufacturing site changes for a drug substance or its intermediates in the drug substance manufacturing process will be addressed in a separate forthcoming guidance on postapproval changes for the drug substance.

2. Site Change for the Drug Product

For a move of the manufacturing site within an existing facility or a move to a new facility on the same campus using similar equipment and manufacturing processes, submission of stability data on the drug product in the new facility prior to implementation is generally not necessary (Table 15).

For a move to a different campus using similar equipment and manufacturing processes, stability data on the drug product in the new facility should be submitted in a supplemental application. Three months of accelerated and available long-term stability data on one to three batches of drug product manufactured in the new site is recommended, depending on the complexity of the dosage form and the existence of a significant body of information (Table 15). A commitment should be made to conduct long-term stability studies on the first or first three production batch(es) of the drug product, depending on the dosage form and the existence of a significant body of information, manufactured at the new site in accordance with the approved stability protocol. If the stability data are satisfactory, the existing expiration dating period may be used.

Table 15 reflects the guidance provided in existing SUPAC documents that address the stability recommendations for the various levels of site change. The stability data package type and filing mechanisms are as indicated in the table. Note that SUPAC guidances and Table 14 currently do not apply to biotechnology/biological products (see 21 CFR 314.70(g) and 601.12).

3. Change in Packaging Site for Solid Oral Dosage Form Drug Products

A stand-alone packaging operation site change for solid oral dosage form drug products using container(s)/closure(s) in the approved application should be submitted as a CBE supplement. No up-front stability data are necessary. The facility should have a current and satisfactory CGMP compliance profile for the type of packaging operation under consideration before submitting the supplement. The supplement should also contain a commitment to place the first production batch and annual batches thereafter on long-term stability studies using the approved protocol in the application and to submit the resulting data in annual reports.

A packaging site change for other than solid oral dosage form drug products is considered a manufacturing site change and the data package that should be submitted for approval is indicated in Section IX.C.2.

4. Change in Testing Laboratory

An analytical testing laboratory site change may be submitted as a CBE supplement under certain circumstances (see *PAC-ATLS: Postapproval Changes, Analytical Testing Laboratory Sites*, CMC 10, April 1998). No stability data are required.

Table 15: Stability Data to Support Postapproval Drug Product Manufacturing Site Changes[a]

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package	
1	a. Manufacturing site change within a facility with the same equipment, SOPs, environmental conditions, controls, personnel (e.g., remodeling an existing building, add-on to an existing facility).	AR	Type 0	
	b. Packaging site change for solid oral dosage form drug products.	CBE	Type 1	
	c. Test laboratory site change to a new location.	CBE	Type 0	
2	Change within a contiguous campus, or between facilities in adjacent city blocks, with the same equipment, SOPs, environmental conditions, controls, personnel: a.*Immediate release solid oral and semisolid dosage forms*	CBE	Type 1	
	b. *Modified release dosage forms*	CBE	Type 2	
3	Manufacturing site change to a different facility with the same equipment, SOPs, environmental conditions, and controls:		SBI[b]	No SBI[b]
	a. *Immediate Release Solid Oral Dosage Forms*	CBE	Type 2	Type 3
	b. *Semisolid Dosage Forms*	CBE	Type 3	Type 3
	c. *Modified Release Dosage Forms*	PA	Type 3	Type 4

[a] Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and, except for changes in testing laboratory, are not covered in this table. In addition, this table does not apply to biotechnology/biological products.

[b] Significant body of information.

D. Change in Formulation of the Drug Product

Historically, all changes in drug product formulation were grouped together and required extensive stability documentation, usually submitted as a prior-approval supplement. An exception was the deletion of a color from a product that could be reported in an annual report without supporting stability data (21 CFR 314.70(d)(4)). Excipients play a critical role in certain complex dosage forms, including semisolid and modified release drug products. Table 16 provides information on stability recommendations to support postapproval formulation changes.[12]

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[12] Please refer to the following guidance for industry: SUPAC-IR (November 1995), *SUPAC-SS (May 1997)*, and *SUPAC-MR (September 1997)* for more detailed information on formulation changes for those specific dosage forms.

Table 16: Stability Data to Support Postapproval Formulation Changes[a]

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package
1	a. *All Dosage Forms*: Deletion or partial deletion of an ingredient intended to affect the color, taste or fragrance of the drug product. b. *Immediate Release Solid Oral and Semisolid Dosage Forms*: The total additive effect of all excipient changes does not exceed 5%, with individual changes within the limits specified in SUPAC-IR and -SS.[b] c. *Semisolid Dosage Forms*: Change in supplier of a structure-forming excipient which is primarily a single chemical entity (purity 95%). d. *Modified Release Dosage Forms*: See SUPAC-MR guidance document for specific information on what excipient quantity changes constitute a level 1 change.	AR	Type 1
2	a. *Immediate Release Solid Oral and Semisolid Dosage Forms*: The total additive effect of all excipient changes is >5-10% with individual changes within the limits specified in SUPAC-IR and -SS.[b]	PA	Type 2
	b. *Semisolid Dosage Forms*: Change in supplier or grade of a structure forming excipient not covered under level 1. c. *Semisolid Dosage Forms*: Change in the particle size distribution of active drug substance, if the drug is in suspension.	CBE	
	d. *Modified Release Dosage Forms*: Change in the technical grade and/or specifications of a nonrelease controlling excipient. e. *Modified Release Dosage Forms*: See SUPAC-MR Guidance document for specific information on what release controlling excipient quantity changes constitute a level 2 change.	PA	see SUPAC-MR
3	a. *All Dosage Forms*: Any qualitative or quantitative change in excipient beyond the ranges noted in the level 2 change. b. *Semisolid Dosage Forms*: Change in the crystalline form of the drug substance, if the drug is in suspension.	PA	SBI[c] No SBI[c] Type 2 Type 3/4 Type3/4 Type 4

[a] Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and are not covered in this table.

[b] Allowable changes in the composition are based on the approved target composition and not on previous Level 1 or level 2 changes in the composition. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are allowed and are excluded from the 10% change limit.

[c] Significant body of information.

E. Addition of a New Strength for the Drug Product

The addition of a new strength for an approved drug product will generally require the submission of a prior-approval supplement. Demonstration of equivalent stability between the approved drug product and the new strength will allow extension of the approved drug product expiration dating to the new strength. Depending on issues specific to the drug product (e.g., dosage form) availability of a significant body of information for the approved dosage form, a Type 2, 3, or 4 stability data package may be appropriate as shown in Table 17. New strengths intermediate to those of an approved drug product may be supported by bracketing/matrixing studies (See Section VII.G. and VII.H.).

Table 17: Stability Data to Support Addition of a New Strength for a Drug Product[a]

Definition of Change	Examples	Filing Documentation	Stability Data Package
New strength of identical qualitative and quantitative composition[b]	a. Addition of a score to an immediate release tablet.	PA	Type 1
	b. Change in the fill of an immediate release hard gelatin capsule.	PA	Type 2
	c. Change in the fill of a hard gelatin capsule containing modified release encapsulated beads.	PA	Type 2
	d. Change in the size of an immediate release tablet or capsule.	PA	Type 3
New strength involving a change in the drug substance to excipient(s) ratio	a. *Simple solutions*	PA	Type 2
	b. *Immediate release solid oral dosage forms*	PA	Type 3
	c. *Semisolid and modified release oral dosage forms*	PA	Type 4

[a] Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and are not covered in this table.

[b] No change in drug substance to excipient(s) ratio from the approved drug product.

F. Change in Manufacturing Process and/or Equipment for the Drug Product

A change limited to the manufacturing process of the drug product, such as a change in the type of equipment used, can be supported by the submission of sufficient data to show that such a change does not alter the characteristics or compromise the stability of the drug product. For information on determining when equipment is considered to be of the same design and operating principle, refer to the Supac-IR/MR draft manufacturing equipment addendum (April 1998). In general, stability data on the drug product demonstrating comparability with and equivalency to the previously approved drug product should be submitted. The submission types and stability data packages shown in Table 18 apply to immediate release solid oral dosage forms and semisolid dosage forms and incorporate the criteria provided by those SUPAC documents. Because additional data may be appropriate for more complex dosage forms, the chemistry review team should be consulted. The standard stability commitment to conduct and/or complete the stability studies on the first three production batches produced by the revised manufacturing process in accordance with the approved stability protocol is necessary. If the data are found acceptable, the approved expiration dating period may be retained.

Submissions for approval of a change of manufacturing site for any portion of the manufacturing process for the drug product are addressed in Section IX.C.

Table 18: Stability Data to Support Manufacturing Process Changes[a]

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package	
			SBI[b]	No SBI[b]
1	Process: Changes in processing parameters such as mixing times, operating speeds within application/validation ranges.	AR	Type 0	
	Equipment: Change from nonautomated to automated or mechanical equipment; or Change to alternative equipment of the same design and operating principles.	AR	Type 1	
2	Process: Changes in processing parameters such as mixing times, operating speeds outside of application/validation ranges:			
	a. *Immediate release solid oral dosage forms*	CBE	Type 1	Type 1
	b. *Semisolid dosage forms*	CBE	Type 2	Type 4
	c. *Modified release dosage forms*	CBE	Type 2	Type 2
	Equipment: Changes to equipment of different design and/or operating principles:			
	a. *Immediate release solid oral dosage forms*	PA	Type 2	Type 3/4
	b. *Semisolid dosage forms*	CBE	Type 2	Type 4
	c. *Modified release dosage forms*	PA	Type 3	Type 4
3	Process: Changes in type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder:			
	a. *Immediate release solid oral dosage forms*	PA	Type 2	Type 3/4
	b. *Modified release dosage forms*	PA	Type 4	Type 4

[a] Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and are not covered in this table. In addition, this table does not apply to biotechnology/biological products.

[b] Significant body of information.

G. Change in Batch Size of the Drug Product

A key question in considering an increase in batch size beyond the production batch size approved in the application is whether the change involves a change in equipment or its mode of operation, or other manufacturing parameters described for the approved batch size. If no equipment change is planned, then the next concern is the size of the change relative to the approved batch size, with larger changes expected to present a greater risk of stability problems in the drug product. Table 19 presents the recommended stability data packages for a variety of batch size situations not involving equipment or mode of operation changes.

If an equipment change is part of the batch size change, please refer to Change in Manufacturing Process of the Drug Product (Section IX.F.).

Table 19: Stability Data to Support Postapproval Batch Size Changes[a]

Level of Change	Definition/Examples	Filing Documentation	Stability Data Package
1	*Solid oral dosage forms* (i.e., tablets, capsules, powders for reconstitution), *semisolid dosage forms, and oral solutions*: A change in batch size up to and including a factor of ten times the size of the pivotal clinical trial/biobatch.	AR	Type 1
2	*Solid oral dosage forms* (i.e., tablets, capsules, powders for reconstitution), *semisolid dosage forms, and oral solutions*: A change in batch size beyond a factor of ten times the size of the pivotal clinical trial/biobatch.	CBE	Type 2

[a] Note that metered dose inhalers and dry powder inhalers, transdermal patches, and sterile aqueous solutions are the subjects of forthcoming guidances and are not covered in this table.

H. Reprocessing of a Drug Product

Stability data submitted in support of reprocessing of a specific batch of a drug product should take into account the nature of the reprocessing procedure and any specific impact that might have upon the existing stability profile of the drug. The expiration dating period for a reprocessed batch should not exceed that of the parent batch, and the expiration date should be calculated from the original date of manufacture of the oldest batch.

The acceptability of reprocessing of a specific batch of a drug product will depend on the nature of the reprocessing procedure, which can range from repackaging a batch when packing equipment malfunctions to regrinding and recompressing tablets. The appropriate chemistry review team should be contacted to determine whether or not the reprocessing procedure is acceptable. Any batch of the drug product that is reprocessed should be placed on accelerated and long-term stability studies using the approved protocol to generate a Type 2 stability data package.

I. Change in Container and Closure of the Drug Product

The stability data packages for changes in container and closure of a drug product vary (Table 20). The first factor used in determining the stability data package recommendation is whether or not the protective properties of the container/closure system are affected by the proposed change. Protective properties of the container/closure system include, but are not limited to, moisture permeability, oxygen permeability, and light transmission. Changes that may affect these properties should be supported by a greater amount of data to support the change. The second factor is the nature of the dosage form itself. A solid dosage form will generally be less affected by a container change than a liquid dosage form. Because considerably more information will be needed to document a container/closure change than just stability data, applicants are encouraged to consult with the appropriate chemistry review team to determine the appropriate filing mechanisms. Please refer to the guidance for industry*: Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics* for qualification and quality control information requested for container closure systems.[13] Table 20 below describes what type of stability data should be supplied for some of the most common post-approval changes to container/closure systems for solid and liquid oral drug products.

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[13] A forthcoming guidance will deal more extensively with postapproval packaging changes for all dosage forms.

Table 20: Stability Data to Support Postapproval Container/Closure Changes for Solid and Liquid Oral Drug Products[a]

Type of change	Definition	Examples	Stability Data Package
Changes that do not affect the protective properties of the container/closure system	1. Closure changes	Adding or changing a child-resistant feature to a packaging system or changing from a metal to a plastic screw cap, while the inner seal remains unchanged.	Type 0
	2. Changing the secondary packaging	Changing a carton.	Type 0
	3. Removal of non-drug product material	Removing: a. an insert. b. a filler.	Type 0 Type 1
	4. Changing shape of container/closure	(Without changing the size)	Type 0
	5. Changing size of container/closure	a. Within the approved range of sizes. b. Outside the approved range of sizes.	Type 0 Type 2
Changes that may affect the protective properties of the container/closure system	1. Adding or changing a component to increase protection within the same system.	a. Adding, or changing to, a heat-induction seal: i. For a solid oral drug product. ii. For a liquid oral drug product. b. Adding or changing a desiccant or a filler. c. Adding an overwrap or carton.	Type 1 Type 2 Type 2 Type 2
	2. Changing the manufacturer or formulation of a container/closure component, including bottle or blister resin, cap liner, seal laminate, desiccant, filler, etc., within the same system.	a. Using an approved or compendial container or closure equivalency protocol for: i. a solid oral drug product. ii. a liquid oral drug product. b. Without an approved or compendial container or closure equivalency protocol.	Type 1 Type 1 Type 2
	3. Changing to a different container and closure system	For any solid or liquid oral drug product.	SBI[b] Type 3 No SBI[b] Type 4

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[a] In certain situations, e.g., for particularly sensitive drug products, additional stability requirements may apply. Note that Metered Dose Inhalers and Dry Powder Inhalers, Transdermal Patches, and Sterile Aqueous Solutions are the subject of a forthcoming guidance and are not covered in this table.

[b] Significant body of information.

J. Changes in the Stability Protocol

In general, modification of the approved stability protocol is discouraged until the expiration dating period granted at the time of approval has been confirmed by long-term data from production batches. However, changes in analytical methods provide increased assurance in product identity, strength, quality, and purity, or to comply with USP monographs, may be appropriate prior to the confirmation of the expiration dating period.

Certain parameters may be reduced in test frequency or omitted from the stability protocol for annual batches on a case-by-case basis through a prior-approval supplement. A justification for such a reduction or omission should be adequately provided.

If justified, test frequency for all parameters may be reduced for *annual batches* based on accumulated stability data. Such a modification to the approved stability protocol should be submitted as a prior-approval supplement. The justification may include a demonstrated history of satisfactory product stability, which may in turn include, but not be limited to, full long-term stability data from at least three production batches. The reduced testing protocol should include a minimum of four data points, including the initial time point, and the expiry and two points in between. For example, drug products with an expiration dating period of less than 18 months should be tested at quarterly intervals; products with an expiration dating period of 18 but not more than 30 months should be tested semiannually; and products with an expiration dating period of 36 months or longer should be tested annually. It should be noted, however, that the reduced testing protocol applies only to annual batches and does not apply to batches used to support a postapproval change that requires long-term stability data at submission and/or as a commitment. Furthermore, whenever product stability failures occur, the original full protocol should be reinstated for annual batches until problems are corrected.

A bracketing or matrixing design, if proposed for annual batches or to support a supplemental change, should be submitted as a prior-approval supplement (see Sections VII.G. and H.). It is acceptable to submit these modifications to the protocol, along with data generated therefrom to support a supplemental change, in one combined prior-approval supplement. However, the applicant is encouraged to consult with the appropriate FDA chemistry review team before initiating such studies.

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GLOSSARY

Accelerated Testing [ICH Q1A]

Studies designed to increase the rate of chemical degradation or physical change of an active drug substance and drug product by using exaggerated storage conditions as part of the formal, definitive, stability protocol. These data, in addition to long-term stability data, may also be used to assess longer term chemical effects at nonaccelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Acceptance Criteria [21 CFR 210.3]

Product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Active Substance; Active Ingredient; Drug Substance; Medicinal Substance [ICH Q1A]

The unformulated drug substance which may be subsequently formulated with excipients to produce the drug product.

Approved Stability Protocol

The detailed study plan described in an approved application to evaluate the physical, chemical, biological, and microbiological characteristics of a drug substance and a drug product as a function of time. The approved protocol is applied to generate and analyze acceptable stability data in support of the expiration dating period. It may also be used in developing similar data to support an extension of that expiration dating period, and other changes to the application. It should be designed in accordance with the objectives of this guidance.

Batch [21 CFR 210.3(b)(2)]

A specific quantity of a drug 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.

Bracketing ICH Q1A]

The design of a stability schedule so that at any time point only the samples on the extremes, for example, of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples is represented by those at the extremes.

Climatic Zones [ICH Q1A]

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.

Complex Dosage Form

A complex dosage form is one where quality and/or stability is more likely to be affected by changes because the release mechanism, delivery system, and manufacturing process are more complicated and thus more susceptible to variability.

Examples of complex dosage forms include modified-release dosage forms, metered-dose inhalers, transdermal patches, liposome preparations. Due to the diversity of currently marketed dosage forms and the ever-increasing complexity of new delivery systems, it is impossible to clearly identify simple vs. complex dosage forms in an exhaustive manner. Applicants are advised to consult with the appropriate FDA chemistry review team when questions arise.

Conjugated Product [ICH Q5C]

A conjugated product is made up of an active ingredient (e.g., peptide, carbohydrate) bound covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

Confirmatory Studies [ICH Q1B]

Those studies undertaken to establish photostability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light-resistant packaging and/or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batch(es) should be selected according to batch selection for long-term and accelerated testing which is described in the parent guidance.

Controlled Room Temperature (CRT) [USP]

A temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C (68°F to 77°F) that results in a mean kinetic temperature (MKT) calculated to be not more than 25°C and that allows for excursions between 15°C and 30°C (59°F to 86°F) that are experienced in pharmacies, hospitals and warehouses.

Date of Production

The date that the first step of manufacture is performed which involves the combining of an active ingredient, antioxidant, or preservative, with other ingredients in the production of a dosage form. For drug products consisting of a single ingredient filled into a container, the date of the production is the initial date of the filling operation. For a biological product subject to licensure see the definition of date of manufacture in 21 CFR 610.50.

Degradation Product [ICH Q5C]

A molecule resulting from a change in the drug substance bulk material) brought about over time. For the purpose of stability testing of the products described in this guidance, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biotechnological/biological products, some degradation products may be active.

Dosage Form; Preparation [ICH Q1A]

A pharmaceutical product type, for example tablet, capsule, solution, cream, that contains a drug substance, generally, but not necessarily, in association with excipients.

Drug Product; Finished Product [ICH Q1A]

The dosage form in the final immediate packaging intended for marketing.

Drug Substance; Active Substance [21 CFR 312.3(b)]

An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body.

Excipient [ICH Q1A]

Anything other than the drug substance in the dosage form.

Expiry/Expiration Date [ICH Q1A]

The date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used.

Extractables/Leachables

Materials or components derived from the container/closure which have been transferred into the contained drug substance or drug product.

Forced Degradation Testing Studies [ICH Q1B]

Those studies undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

Formal (Systematic) Studies [ICH Q1A]

Formal studies are those undertaken to a preapproval stability protocol which embraces the principles of these guidances.

Immediate (Primary) Pack [ICH Q1B]

That constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Impurity

Any entity of the drug substance (bulk material) or drug product (final container product) that is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

Intermediate [ICH Q5C]

For biotechnological/biological products, a material produced during a manufacturing process that is not the drug substance or the drug product but for which manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications will be established to determine the successful completion of the manufacturing step before continuation of the manufacturing process. This includes material that may undergo further molecular modification or be held for an extended period before further processing.

Long-Term (Real-Time) Testing [ICH Q1A]

Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a drug product and a drug substance, covering the expected duration of the shelf life and retest period, which are claimed in the submission and will appear on the labeling.

Lot [21 CFR 210.3(b)(10)]

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.

Manufacturing-Scale Production [ICH Q5C]

Manufacture at the scale typically encountered in a facility intended for product production for marketing.

Marketing Pack [ICH Q1B]

The combination of immediate pack and other secondary packaging such as a carton.

Mass Balance (Material Balance) [ICH Q1A]

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision.

This concept is a useful scientific guide for evaluating data but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing [ICH Q1A]

The statistical design of a stability schedule so that only a fraction of the total number of samples are tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure, and, possibly, in some cases different containers/closure systems.

Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the FDA chemistry review team where this is possible. In every case, it is essential that all batches are tested initially and at the end of the long-term testing period.

Mean Kinetic Temperature [ICH Q1A]

Mean kinetic temperature (MKT) [14] is defined as the isothermal temperature that corresponds to the kinetic effects of a time-temperature distribution.

Modified Release Dosage Forms [SUPAC-MR]

Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

New Dosage Form [ICH Q1C]

A drug product which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

New Molecular Entity; New Active Substance [ICH Q1A]

A substance which has not previously been registered as a new drug substance with the national or

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[14] J.D. Haynes,"Worldwide Virtual Temperatures for Product Stability Testing", *J. Pharm. Sci*., Vol. 60, No. 6, 927 (June 1971).

regional authority concerned.

Pilot-Plant Scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that to be applied on a full manufacturing scale.

For oral solid dosage forms this is generally taken to be at a minimum scale of one tenth that of full production or 100,000 tablets or capsules, whichever is the larger. [Q1A]

For biotechnology products, the methods of cell expansion, harvest, and product purification should be identical except for the scale of production.
[ICH Q5C]

Primary Stability Data [ICH Q1A]

Data on the drug substance stored in the proposed packaging under storage conditions that support the proposed retest date.

Data on the drug product stored in the proposed container/closure for marketing under storage conditions that support the proposed shelf life.

Production Batch

A batch of a drug substance or drug product manufactured at the scale typically encountered in a facility intended for marketing production.

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.

Reference Listed Drug [21 CFR 314.3]

The listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.

Retest Date [ICH Q1A]

The date when samples of the drug substance should be reexamined to ensure that the material is still suitable for use.

Retest Period [ICH Q1A]

The time interval during which the drug substance can be considered to remain within the specifications and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions; after this period the batch should be retested for compliance with specifications and then used immediately.

Semi-Permeable Container

A container which permits the passage of a solvent, such as water contained therein, but prevents the passage of the dissolved substance or solute, thus resulting in an increased concentration of the latter over time. It may also permit the ingress of foreign volatile materials. The transport of the solvent, its vapor, or other volatile material occurs through the container by dissolution into one surface, diffusion through the bulk of the material, and desorption from the other surface, all caused by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags or semi-rigid LDPE for LVPs, and LDPE ampoules, vials, or bottles for inhalation or ophthalmic solutions.

Semisolid Dosage Forms [SUPAC-SS]

Semi-solid dosage forms include non-sterile and semi-solid preparations, e.g., creams, gels and ointments, intended for all topical routes of administration.

Shelf Life; Expiration Dating Period [ICH Q1A]

The time interval that a drug product is expected to remain within the approved shelf-life specification provided that it is stored under the conditions defined on the label in the proposed containers and closure.

Significant Body of Information [SUPAC-IR/MR]

Immediate Release Solid Oral Dosage Forms

A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.

Modified Release Solid Oral Dosage Forms

A significant body of information should include, for “Modified Release Solid Oral Dosage Forms,” a product-specific body of information. This product-specific body of information is likely to exist after five years of commercial experience for the original complex dosage form drug product, or three years of commercial experience for any subsequent complex dosage form drug product.

Significant Change [ICH Q1A]

Significant change for a drug product at the accelerated stability condition and the intermediate stability condition is defined as:

1. A 5 percent potency loss from the initial assay value of a batch;

2. Any specified degradant exceeding its specification limit;
3. The product exceeding its pH limits;
4. Dissolution exceeding the specification limits for 12 capsules or tablets;
5. Failure to meet specifications for appearance and physical properties, e.g., color, phase separation, resuspendibility, delivery per actuation, caking, hardness.

Simple Dosage Form

A dosage form whose quality and/or stability is less likely to be affected by the manufacturing site because the release mechanism, delivery system, and manufacturing process are less complicated and less susceptible to variability.

Examples of simple dosage forms include immediate-release solid oral dosage forms, e.g., tablets, capsules, semi-solid dosage forms, and oral and parenteral solutions. Due to the diversity of currently marketed dosage forms and the ever-increasing complexity of new delivery systems, it is impossible to clearly identify simple vs. complex dosage forms in an exhaustive manner. Applicants are advised to consult with the appropriate FDA chemistry review team when questions arise.

Site-Specific Batches

Batches of drug substance or drug product made at the intended manufacturing scale production site from which stability data are generated to support the approval of that site, as well as to support the proposed retest period or expiration dating period, respectively, in an application. The site-specific batch(es) of the drug product should be made from identifiable site-specific batch(es) of the drug substance whenever possible.

Specification-Check/Shelf-life [ICH Q1A]

The combination of physical, chemical, biological and microbiological test requirements that a drug substance must meet up to its retest date or a drug product must meet throughout its shelf life.

Specification-Release [ICH Q1A]

The combination of physical, chemical, biological and microbiological test requirements that determine that a drug product is suitable for release at the time of its manufacture.

Stability

The capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period, as appropriate.

Stability Commitment

A statement by an applicant to conduct and/or complete prescribed studies on production batches of a drug product after approval of an application.

Stability-Indicating Methodology

Validated quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.

Stability Profile

The physical, chemical, biological, and microbiological behavior of a drug substance or drug product as a function of time when stored under the conditions of the Approved Stability Protocol.

Storage Conditions Tolerances [ICH Q1A]

The acceptable variation in temperature and relative humidity of stability storage.

Strength [21 CFR 210.3(b)(16)]

The concentration of the drug substance (for example weight/weight, weight/volume, or unit dose/volume basis), and/or the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory test or by adequately developed and controlled clinical data (expressed for example, in terms of units by reference to a standard).

Stress Testing - Drug Substance [ICH Q1A]

Studies undertaken to elucidate intrinsic stability characteristics. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated tests.

Stress Testing - Drug Product [ICH Q1A]

Light testing should be an integral part of stress testing.

Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Supporting Stability Data [ICH Q1A]

Data other than the primary stability data, such as stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support to the analytical procedures, the proposed retest period or shelf life and storage conditions.

Tentative Expiration Dating Period

A provisional expiration dating period which is based on acceptable accelerated data, statistical analysis of available long-term data, and other supportive data for an NDA product, or on acceptable accelerated data for an ANDA product, but not on full long-term stability data from at least three production batches.