F. Submission and Deadline

Submit the original and two copies of PHS 5161–1 (OMB Number 0937–0189).

By May 1, 2000, submit the application to the Grants Management Specialist identified in the ''Where to Obtain Additional Information'' section of this announcement.

1. Deadline: Applications will be considered as meeting the deadline if they are either:

a. Received on or before the stated deadline date; or

b. Sent on or before the deadline date. (Applicants must request a legibly dated U.S. Postal Service postmark or obtain a legibly dated receipt from a commercial carrier or the U.S. Postal Service.

Private metered postmarks shall not be acceptable proof of timely mailing.)

2. Late Applications: Applications which do not meet the criteria in 1(a) or 1(b) above are considered late applications and will be returned to the applicant.

G. Evaluation Criteria

The application will be evaluated according to the following criteria by an independent review group appointed by CDC.

1. Need statement. The extent to which the applicant identifies specific opportunities and existing gaps related to the purpose of the program. (10 points)

2. Objectives. The degree to which short- and long-term objectives are specific, measurable, attainable, time phased, and realistic. (20 points)

3. Operational Plans. The adequacy of the applicant's plan to carry out the proposed activities, including the extent to which the applicant plans to work collaboratively with other organizations and individuals who may have an impact on cancer prevention and control objectives. (25 points)

4. Evaluation Plan. The extent to which the evaluation plan appears capable of monitoring progress toward meeting project objectives. (25 points)

5. Program Management. The extent to which proposed staff appear to be qualified and possess capacity to perform the project. (20 points)

6. Budget. The extent to which each line-item budget and narrative justification for Projects 1, 2, 3 and 4 are reasonable and consistent with the purpose and objectives of the program. (Not weighted)

7. Human Subjects. Does the application adequately address the requirements of Title 45 CFR Part 46 for the protection of human subjects? (Not Weighted)

8. The degree to which the applicant has met the CDC Policy requirements regarding the inclusion of women, ethnic, and racial groups in the proposed research. This includes:

1. The proposed plan for the inclusion of both sexes and racial and ethnic minority populations for appropriate representation.

2. The proposed justification when representation is limited or absent.

3. A statement as to whether the design of the study is adequate to measure differences when warranted.

4. A statement as to whether the plans for recruitment and research for study participants include the process of establishing partnerships with community(ies) and recognition of mutual benefits.

H. Other Requirements

Technical Reporting Requirements

Provide CDC with the original plus two copies of the following:

1. Annual written progress report must be submitted 30 days after the end of each budget period.

2. Financial status report (FSR) must be submitted 90 days after the end of each budget period.

3. Final financial and performance reports, must be submitted 90 days after the end of the project period.

Send all reports to the Grants Management Specialist identified in the ''Where to Obtain Additional Information'' section of this announcement.

The following additional requirements are applicable to this program. For a complete description of each, see Attachment I in the application package.

AR–1 Human Subjects Requirement
AR–2 Requirements for Inclusion of Women and Racial and Ethnic Minorities in Research
AR–9 Paperwork Reduction Act Requirements
AR–10 Smoke-Free Workplace Requirements
AR–11 Healthy People 2010
AR–12 Lobbying Restrictions
AR–20 Conference Support

I. Authority and Catalog of Federal Domestic Assistance Number

This program is authorized under sections 301(a), 317(k)(2) of the Public Health Service Act [42 U.S.C. 241(a) and 247b(k)(2)], as amended. The Catalog of Federal Domestic Assistance Number for this program is 93.283.

J. Where To Obtain Additional Information

To obtain additional information contact: Nealean K. Austin, Grants Management Specialist Grants Management Branch, Procurement and Grants Office Announcement 00037 Centers for Disease Control and Prevention (CDC) Room 3000, 2920 Brandywine Road, Atlanta, GA 30341, telephone (770)–488–2754, E-mail address nea1@cdc.gov

See also the CDC home page on the Internet: http://www.cdc.gov

For program technical assistance, contact: Corinne Graffunder, Chief, Section A, Program Services Branch, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC), 4770 Buford Highway, NE., Mailstop K–57, Atlanta, GA 30341–3724, telephone (770) 488–4880, fax (770) 488–3230.

Dated: April 17, 2000.

John L. Williams,

Director, Procurement and Grants Office, Centers for Disease Control and Prevention (CDC).

[FR Doc. 00–9956 Filed 4–20–00; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93D–0139]

International Conference on Harmonisation; Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a draft revised guidance entitled ''Q1A(R) Stability Testing of New Drug Substances and Products.'' The draft revised guidance, which updates a guidance on the same topic published in the **Federal Register** of September 22, 1994 (the 1994 guidance), was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The draft revised guidance clarifies the 1994 guidance, adds information, and provides consistency with more recently published ICH guidances. The draft revised guidance is intended to reflect formal scientific principles for stability testing of drugs and should be useful to applicants submitting new drug applications for new molecular entities and associated drug products.

DATES: Submit written comments by June 5, 2000.

ADDRESSES: Submit written comments on the draft revised guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Copies of the draft revised guidance are available from the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4573. Single copies of the draft revised guidance may be obtained by mail from the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), or by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800. Copies may be obtained from CBER's FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Chi Wan Chen, Center for Drug Evaluation and Research (HFD–830), Food and Drug Administration, 9201 Corporate Blvd., Rockville, MD 20850, 301–827–2001.

Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–0864.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industries Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA, and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

In October 1999, the ICH Steering Committee agreed that a draft revised guidance entitled ''Q1A(R) Stability Testing of New Drug Substances and Products'' should be made available for public comment. The draft revised guidance is a revision of an ICH guidance on the same topic published in the **Federal Register** of September 22, 1994 (59 FR 48754). The draft revised guidance is the product of the Quality Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the Quality Expert Working Group.

In accordance with FDA's good guidance practices (62 FR 8961, February 27, 1997), this document is now being called a guidance, rather than a guideline.

The draft revised guidance provides guidance on the information to be submitted in the stability data package for a new drug substance or drug product. The revisions add information on stability storage conditions: (1) For drug substances and products intended to be stored in a refrigerator or freezer and (2) for drug products packaged in semipermeable containers. The revisions clarify the guidance on: (1) Testing frequencies for stability studies at accelerated and intermediate conditions and (2) stability commitments.

The draft revised guidance recognizes certain regional regulatory constraints. The Preamble and Objective sections of the 1994 guidance were revised to recognize that, in some regions, guidance does not constitute a regulatory requirement. The Storage Conditions sections of the 1994 guidance were revised to recognize that, in some regions, stability amendments to pending applications are not permissable.

The draft revised guidance includes references to three recently published ICH guidances: (1) ''Q1B Photostability Testing of New Drug Substances and Products,'' (2) ''Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances,'' and (3) ''Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.''

This draft guidance applies in general to new dosage forms and biotechnological/biological products as does the original Q1A guidance. Additional guidance specific to the stability testing of new dosage forms and biotechnological/biological products can be found in two previously published ICH guidances entitled ''Q1C: Stability Testing of New Dosage Forms'' and ''Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products,'' respectively.

This draft revised guidance represents the agency's current thinking on stability testing of new 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 approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft revised guidance on or before June 5, 2000. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft revised guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. An electronic version of this guidance is available on the Internet at http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/publications.htm.

The text of the draft revised guidance follows:

Q1A(R): Stability Testing of New Drug Substances and Products [1]

Preamble

The following guidance defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover

[1] This draft revised guidance represents the agency's current thinking on stability testing of new 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 approach satisfies the requirements of the applicable statute, regulations, or both.

the testing for registration in or export to other areas of the world.

The principle that stability information generated in any one of the three regions of the EC, Japan, and the United States would be mutually acceptable in both of the other two regions has been established, provided the information is consistent with this guidance and the labeling is in accord with national/regional requirements.

The guidance seeks to exemplify the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches may be used when there are scientifically justifiable reasons.

Specific details of the sampling and testing for particular dosage forms/packaging, etc., are not covered in this guidance.

Objective

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, and enables recommended storage conditions, retest periods, and shelf lives to be established.

Scope

The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the three areas of the EC, Japan, and the United States. 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).

Drug Substance

General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Stress Testing

Stress testing helps determine the intrinsic stability of the molecule by establishing degradation pathways in order 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. The severe conditions that may be encountered during distribution can be covered by stress testing. 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 material and to include the effect of temperatures in 10 degrees Celsius (°C) increments (e.g., 50 °C, 60 °C) above the accelerated temperature test condition and humidity (e.g., 75 percent RH or greater) where appropriate and oxidation and photolysis on the drug substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension.

Photostability testing should be an integral part of stress testing. (The standard conditions for photostability testing are defined in ICH Q1B.)

It is recognized that some degradation pathways can be complex and that, under forcing 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.

Results from these studies will form an integral part of the information provided to regulatory authorities.

Selection of Batches

Data from formal stability studies should be provided on at least three batches of the drug substance. The batches manufactured to a minimum of pilot 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 formal stability studies should be representative of the quality of the material used in clinical studies and of the quality of material to be made on a manufacturing scale.

Supporting stability data may be provided using stability data generated from batches of drug substance made on a laboratory scale.

Packaging/Containers

The stability studies should be conducted on material stored in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

Test Attributes, Test Procedures, and Test Acceptance Criteria

Test attributes, test procedures, and acceptance criteria are defined in ICH Q6A and Q6B.

The testing should cover attributes of the drug substance susceptible to change during storage and likely to influence quality, safety, and/or efficacy. Stability information should cover, as appropriate, the physical, chemical, biological, and microbiological attributes of the drug substance. Validated stability-indicating test procedures should be applied. The need for and extent of replication will depend on the results from validation studies.

Acceptance criteria are numerical limits, ranges, and other criteria for the specific tests described and should include individual and total upper limits for impurities and degradation products. The acceptance criteria should be derived from batches of the material used in the preclinical and clinical studies.

Testing Frequency

Frequency of testing should be sufficient to establish the stability attributes of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition will normally be every 3 months over the first year, every 6 months over the second year, and then annually.

For the accelerated storage conditions, a minimum of three test points, including the initial and end points (e.g., 0, 3, and 6 months) is recommended. Where an expectation (based on development experience) exists that results from accelerated storage are likely to approach significant change criteria, increased testing should be conducted either by testing additional samples at the final time point or by inclusion of a fourth time point in the protocol.

When testing at the intermediate storage condition is necessary as a result of failure at the accelerated storage condition, a minimum of four test points, including the initial and end points, is recommended (e.g., 0, 6, 9, and 12 months).

Storage Conditions

In general, a drug substance should be evaluated for stability as appropriate under storage conditions that test both thermal stability and stability at conditions of elevated humidity. The storage conditions and length of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The storage condition at which long-term testing is conducted will be reflected in the labeling and retest date. The long-term testing should cover a minimum of 12 months' duration at the time of submission and should be continued for a sufficient period to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition or from the intermediate storage condition, as appropriate, may be used to evaluate the impact of short-term excursions outside the label storage conditions (such as might occur during shipping).

Significant change is defined as failure to meet the specification.

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. Alternative storage conditions are allowable if justified. If not covered by a subsequent section, a drug substance should be considered as belonging to the general case.

General Case for Drug Substances

Study	Storage Condition	Minimum Time Period at Submission
Long-term	25 °C ± 2 °C/60% RH ± 5% RH	12 months
Intermediate	30 °C ±2 °C/60% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

When ''significant change'' occurs at any time during 6 months' storage at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Drug Substances Intended for Storage in a Refrigerator

Study	Storage Condition	Minimum Time Period at Submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real-time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, data should be supplied to cover use of the drug substance outside of the label storage condition. It is not necessary to continue to test a product to 6 months when an obvious significant change has occurred within the first 3 months.

Drug Substances Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period at Submission
Long-term	−20 °C ± 5 °C	12 months

For drug substances intended for storage in a freezer, the retest period should be based on the real-time data presented at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing at an elevated temperature (e.g., 5 °C ± 3 °C or 25 °C ± 2 °C) on a single batch should be conducted to support use of the drug substance outside of the proposed label storage condition.

Drug Substances Intended for Storage Below −20 °C

Drug substances intended for storage below −20 °C should be treated on a case-by-case basis.

Stability Commitment

When available long-term stability data on primary batches do not cover the proposed retest period granted at the time of approval, the studies should be continued postapproval in order to firmly establish the retest period.

Where the submission includes long-term storage data from three production batches covering the proposed retest period, no postapproval commitment is necessary. Otherwise, the appropriate alternative from those shown below should be followed:

1. If the submission includes stability data on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.

2. If the submission includes stability data on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed retest period.

3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed retest period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches unless otherwise scientifically justified.

Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (covering as appropriate the physical, chemical, biological, and microbiological attributes), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period.

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 these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a full justification for the omission would be sufficient.

An acceptable approach for quantitative characteristics that are expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean degradation curve intersects the acceptable 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 (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 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.

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.

Limited extrapolation of the real-time data from the long-term testing storage condition beyond the observed range to extend the retest period at approval time may be undertaken, particularly where the accelerated data support this. However, this assumes that the same degradation relationship will continue to apply beyond the observed data. Hence the use of

extrapolation should be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

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 instructions should be provided, particularly for drug substances that cannot tolerate freezing. The use of terms such as ''ambient conditions'' or ''room temperature'' is unacceptable.

A retest period should be derived from the stability information.

Drug Product

General

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and on experience gained from clinical formulation studies and from stability studies on the drug substance. The likely changes on storage and the rationale for the selection of attributes to test in the formal stability studies should be stated.

Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. (The standard conditions for photostability testing are defined in ICH Q1B.)

Selection of Batches

Data from formal stability studies are to be provided on at least three batches of the drug product. 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 manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meet the same quality specification as that intended for marketing. Where possible, batches of the drug product should be manufactured using different batches of drug substance.

Laboratory scale batches are not acceptable for formal stability studies. Data on associated formulations or packaging may be submitted as supporting stability data.

Packaging/Containers

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

Test Attributes, Test Procedures, and Acceptance Criteria

Test attributes, test procedures, and acceptance criteria, including the concept of release and shelf life specifications, are defined in ICH Q6A and Q6B.

The testing should cover those attributes 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 and extent of replication will depend on the results of validation studies.

The range of testing should cover, as appropriate, chemical and/or biological stability, loss of preservative, physical properties, characteristics, functionality, and microbiological attributes.

Acceptance criteria should relate to the release limits (where applicable) to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable differences from the release specification based on the stability evaluation and the changes observed on storage. It should 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, should reference the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

Testing Frequency

Frequency of testing should be sufficient to establish the stability attributes of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition will normally be every 3 months over the first year, every 6 months over the second year, and then annually.

For the accelerated storage conditions, a minimum of three test points, including the initial and end points (e.g., 0, 3, and 6 months), is recommended. Where an expectation (based on development experience) exists that results from accelerated storage are likely to approach significant change criteria, increased testing should be conducted either by testing additional samples at the final time point or by inclusion of a fourth time point in the protocol.

When testing at the intermediate storage condition is necessary as a result of failure at the accelerated storage condition, a minimum of four test points, including the initial and end points is recommended (e.g., 0, 6, 9, and 12 months).

Matrixing or bracketing can be applied, if justified. (See Glossary.)

Storage Conditions

In general, a drug product should be evaluated under storage conditions that test the thermal stability and, if appropriate, its sensitivity to moisture or, for liquid products in semipermeable containers, potential for solvent loss. The storage conditions and length of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

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

The storage condition at which long-term testing is conducted will be reflected in the labeling and expiration date. The long-term testing should cover a minimum of 12 months' duration at the time of submission and should be continued for a sufficient period to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition or from the intermediate storage condition as appropriate may be used to evaluate the impact of short-term excursions outside the label storage conditions (such as might occur during shipping).

In general, significant change is defined as:

1. A 5 percent potency change from the initial assay value;
2. Any specified degradant exceeding its acceptance criteria;
3. Failure to meet acceptance criteria for appearance and physical properties (e.g., color, phase separation, resuspendibility, delivery per actuation, caking, hardness); and as appropriate to the product type;
4. The pH exceeding its acceptance criteria; and
5. Dissolution exceeding the acceptance criteria for 12 dosage units.

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below; alternative storage conditions are allowable if justified. If not covered by a subsequent section, a drug product should be considered as belonging to the general case.

General Case

Study	Storage Condition	Minimum Time Period at Submission
Long-term	25 °C ± 2 °C/60% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/60% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

When ''significant change'' occurs at any time during 6 months' storage at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Drug Products Stored in Impermeable Containers

The sensitivity to moisture or the potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent, e.g., semisolids in sealed aluminum tubes, solutions in sealed glass ampules. Thus, stability studies for products stored in impermeable containers may be conducted under any relative humidity.

Drug Products Packaged in Semipermeable Containers

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity as discussed below. Other comparable approaches may be developed and reported for nonaqueous, solvent-based products.

Ultimately, the shelf life for aqueous-based drug products stored in semipermeable containers should justify storage in low relative humidity environments. To accommodate this, it should be demonstrated that the drug product will remain within its approved acceptance criteria throughout the proposed shelf life if stored at a temperature of 25 °C and at the reference relative humidity of 40 percent RH.

Study	Storage Condition	Minimum Time Period at Submission
Long-term	25 °C ± 2 °C/40% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/60% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months (water loss after 3 months)

An acceptable alternative approach to storage at the reference reduced humidity (for both long-term and accelerated storage) is to perform the stability studies under higher relative humidity and to derive the water loss at reduced relative humidity through calculation. This may be done by experimentally determining the permeation coefficient for the container and closure system or the ratio of water loss between the two humidity conditions at the same temperature as shown in the example below. The permeation coefficient for any packaging system may be experimentally determined to cover a worst case alternative relative to the proposed drug product.

A significant change in water loss for a product packaged in a semipermeable container has occurred when there has been a water loss of greater than 5 percent after 3 months' storage equivalent to 40 °C/NMT 25 percent RH. However, for small single-dose products, a water loss of greater than 5 percent after 3 months' storage equivalent to 40 °C/NMT 25 percent RH may be acceptable if justified.

A significant change in water loss alone will not necessitate testing at the intermediate storage condition.

Example Approach for Determining Percentage Water Loss

An appropriate approach for calculating an equivalent percentage water loss for a product stored at a reference relative humidity from data generated from an alternative relative humidity at the same temperature is described below. A linear rate of moisture loss over the storage period should be demonstrated.

A mean percentage weight loss at the reference relative humidity should be calculated from that measured at the alternative relative humidity at a given temperature after a specified storage period.

For example, the equivalent weight loss after 3 months' storage at NMT 25 percent RH (at 40 °C) is the product of the percentage weight loss at 75 percent RH (at 40 °C) after 3 months, multiplied by 3.0 from the table below.

Other valid calculated relative humidity ratios than those in the table below may also be used.

Alternative Humidity	Nominated Humidity	Ratio
60% RH	25% RH	2.4
60% RH	40% RH	1.5
75% RH	25% RH	3.0

Drug Products Intended for Storage in a Refrigerator

Study	Storage Condition	Minimum Time Period at Submission
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real-time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, data should be supplied to cover use of the drug product outside of the label storage condition. It is not necessary to continue to test a product to 6 months when an obvious significant change has occurred within the first 3 months.

Drug Products Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period at Submission
Long-term	−20 °C ± 5 °C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real-time data presented at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, data from elevated temperature (e.g., 5 °C ± 3 °C or 25 °C ± 2 °C) on a single batch should be obtained to support use of the drug product outside of the proposed label storage condition.

Drug Products Intended for Storage Below −20 °C

Drug products intended for storage below −20 °C should be treated on a case-by-case basis.

Stability Commitment

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, the studies should be continued postapproval in order to firmly establish the shelf life.

Where the submission includes long-term storage data from three production batches covering the proposed shelf life, no postapproval commitment is necessary. Otherwise, the appropriate alternative from those shown below should be followed.

1. If the submission includes stability data on at least three production batches, a commitment should be made to continue these studies through the proposed shelf life.
2. If the submission includes stability data on fewer than three production batches, a commitment should be made to continue these studies through the proposed shelf life and to place additional production batches, to a total of at least three, on long-term and accelerated stability studies through the proposed shelf life.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term and accelerated stability studies through the proposed shelf life.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches unless otherwise scientifically justified.

Where a significant change has occurred at the accelerated storage condition for the primary batches, testing on the commitment batches should be conducted at the intermediate storage condition instead of the accelerated storage condition. As an alternative, testing may be conducted at the accelerated storage condition for the commitment batches. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

Evaluation

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

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; providing a justification for the omission should be sufficient.

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

An acceptable approach for quantitative characteristics that are expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean degradation curve intersects the acceptance criterion. 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 (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 it is inappropriate to combine data from several batches, the overall shelf life 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 on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data presented from the long-term storage condition beyond the observed range to extend the shelf life at approval time, particularly where the accelerated data support this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation should be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

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

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 product. Where applicable, specific instruction should be provided, 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.

Annex 1

Glossary and Information

The following terms have been in general use, and the following definitions are provided to facilitate interpretation of the guidance.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. These data, in addition to long-term stability studies, 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.

Bracketing: 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 are represented by those at the extremes.

Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of immediate containers is to be evaluated,

bracketing designs may be applicable if the composition of the container and the type of closure are the same throughout the range.

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

Commitment batches: Production batches of a drug substance or drug product for which the stability studies will be initiated or completed postapproval through a commitment made in the registration application.

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

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the drug product.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: 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.

Formal stability studies: Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents.

Long-term testing: Stability studies under the recommended storage condition, for the retest period or shelf life proposed (or approved) for labeling.

Mass balance: The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical error.

Matrixing: The statistical design of a stability schedule so that only a fraction of the total number of samples is 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 container/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 being 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 regulatory authority, 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.

Mean kinetic temperature: A single derived temperature that, if maintained over a defined period, affords the same thermal challenge to a drug substance or drug product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.* 60:927–929, 1971) can be used.

New molecular entity: A substance that has not previously been registered as a new drug substance with the national or regional authority concerned.

Pilot 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 solid oral 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.

Primary batch: A batch of drug substance or drug product used in a formal stability study from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch should be at least a pilot scale batch (except in the case of drug product where one of the three batches can be smaller); but it may also be a production batch.

Production batch: A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still suitable for use.

Retest period: The period of time during which the drug substance can be considered to remain within the specification 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, a batch destined for use in the manufacture of a drug product should be retested for compliance with specifications and then used immediately.

Semipermeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals, and LDPE ampules, bottles, and vials.

Shelf life: 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.

Specification: See ICH Q6A and Q6B.

Specification—release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification—shelf life: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period or that a drug product should meet throughout its shelf life.

Storage conditions tolerances: The acceptable variation in temperature and relative humidity of storage facilities.

The equipment should be capable of controlling the storage condition within the ranges defined within the body of this document. The actual temperature and humidity 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 the defined tolerances for more than 24 hours should be described in the study report and their impact assessed.

Stress testing (Drug substance): Studies undertaken to elucidate intrinsic stability attributes. 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): Photostability testing should be an integral part of stress testing (see ICH Q1B).

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

Supporting stability data: Data other than from formal stability studies, 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 the analytical procedures, the proposed retest period or shelf life and storage conditions.

Footnote

This guidance has been developed within the Quality Expert Working Group of the ICH Process. Additional topics continue to be discussed within the Expert Working Group and will be the subject of future guidance documents.

Dated: April 14, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00–9942 Filed 4–20–00; 8:45 am]

BILLING CODE 4160–01–F