

**Aventis Pharmaceuticals**



August 1, 2002

Via fax and UPS

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. 02D-0237**

Draft Guidance Q1E Evaluation of Stability Data [67FR 40949, June 14, 2002]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. would like to thank you for the opportunity to comment on the above-referenced draft guidance entitled "Q1E Evaluation of Stability Data".

This draft guidance is an annex to an ICH guidance entitled "Q1A(R) Stability testing of New Drug Substances and Products". The draft guidance is intended to provide recommendations on how to use stability data, generated in accordance with the principles outlined in Q1A(R), to propose a retest period for the drug substance and a shelf life for the drug product.

The development of the draft guidance on evaluation of stability data is welcomed. The underlying principles are generally sound and acceptable. We offer the following comments/clarification for your consideration.

## **1. INTRODUCTION**

### **1.3 Scope of the Guideline**

*Page 1*

*This guideline, an annex to the parent guideline, is intended to provide a clear explanation of expectations when proposing a retest period or shelf life and storage conditions based on the evaluation of stability data for both quantitative and qualitative test attributes. This guideline outlines recommendations for establishing a retest period or shelf life based on stability data from single or multi-factor and full or reduced-design studies.*

020-0237

CS

Since the proposed Q1E guidance is an annex to the parent guideline “Q1A(R) Stability Testing of New Drug Substances and Products”, it should be emphasized that Q1E primarily applies to stability data available at the submission time of the original application for new drug substances and products.

We propose rewording this paragraph as follows: *“This guideline outlines recommendations for establishing a retest period or shelf life for **New Drug Substances and associated Products** based on stability data from single or multi-factor and full or reduced-design studies.”*

We suggest to extend the scope of the proposed Q1E guidance to new formulations of already approved medicines (Q1C guideline “Stability Testing for New Dosage Forms”).

## **2. GUIDELINES**

### **2.1 General Principles**

*Page 1 – second paragraph, second sentence*

*Where appropriate, attention should be paid to reviewing the adequacy of the mass balance.*

We believe that clarification should be provided as to what the “*where appropriate*” refer to.

*Page 2 – fourth paragraph, third sentence*

*Appendix B also provides information on how to use regression analysis for retest period or shelf life estimation and examples of statistical procedures to determine poolability of data from different batches or other factors.*

We believe that details on poolability (e.g. definition of poolability, recommendations on when poolability could apply) should be given not only in the examples in Appendix B but also in the text of the proposed Q1E guidance.

### **2.4 Data Evaluation for Retest Period or Shelf life Estimation for Drug Substances or Products Intended for “Room Temperature” Storage**

*Page 3*

A cross-reference to Appendix A should be added. We propose to add the same sentence as the one used in section 2.5.1 “**A decision tree is provided in Appendix A as an aid to the guidance below**”.

#### **2.4.1 No significant Change at Accelerated Condition**

**2.4.1.1 Long-term and accelerated data showing little or no change over time and little or no variability**

**2.4.1.2 Long-term or accelerated data showing change over time and variability**

Page 3

We believe that clarification should be provided as to what “change” and “significant change” refer to. We suggest to use the term “**acceptable change**”, defined as a change within the acceptance criteria, in contrast with “*significant change*.”

#### **2.4.2 Significant change at accelerated condition**

Page 4 – second paragraph

*\*The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change (potential interaction effects should also be considered in establishing that there is no other significant change): (1) softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated; and (2) failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if it can be unequivocally attributed to cross-linking. However, phase separation of semisolid dosage forms at the accelerated condition could call for testing at the intermediate condition.*

Because the clarification given in this paragraph primarily provides instruction on how to perform stability study, and not on how to evaluate stability data, we propose to add this paragraph to the definition of significant change in the parent guideline Q1A(R).

#### **2.5 Data Evaluation for Retest Period or Shelf life Estimation for Drug Substances or Products Intended for Storage Below “Room Temperature”**

**2.5.1.1 No significant change at accelerated conditions for products intended for refrigerated storage**

Page 5 – second sentence

*The proposed retest period or shelf life can be up to one and a half times the length of available long-term data, but should not exceed the length of available long-term data by more than 6 months.*

For dosage forms such as solutions or suspensions, the risk of physical changes (e.g. precipitation) are not easily predictable based on accelerated testing. Therefore, for these dosage forms, the extrapolation approach should be more restrictive under refrigerated conditions than under for room temperature.

We believe that for less critical dosage forms such as tablets or powders, it should be possible to extrapolate retest period or shelf life up to twice the length of the available long-term data without exceeding the length of available long-term data by more than 12 months. This would be in line with the recommendation provided in section 2.4.1 for drug substances and drug products intended for room temperature storage.

## **Appendix A: Decision Tree for data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding frozen products)**

Page 7

*Significant change within 3 months?*

To be consistent with section 2.5.1, for drug substances and products intended to be stored in a refrigerator, it should be specified after “*Significant change within 3 months?*” “**at accelerated condition?**”.

*No extrapolation; shorter retest period or shelf life and data covering excursions can be called for; statistical analysis if long-term data show variability*

For drug substances and products intended to be stored in a refrigerator, with significant change within 3 months at accelerated condition, the statement “*shorter retest period or shelf life and data covering excursions can be called for; statistical analysis if long-term data show variability*” requires clarification. Is the shorter retest period or shelf life to be decided on request of an authority only?

*If supported by supporting data:  $Y = \text{up to } 1.25 X$ , but no exceeding  $X + 3 \text{ months}$*

For drug substances and products not to be stored in a refrigerator, with significant change at accelerated condition, no significant change at intermediate condition and no statistical analysis performed, the limitation  $Y = \text{up to } 1.25 X$  should be mentioned and explained in section 2.4.2.1 Data not amenable to statistical analysis.

## **Appendix B: Examples of Statistical Approaches to Stability data Analysis**

*Page 8*

This appendix describes options rather than real examples and provides recommendations (i.e. see sentences with “should”).

We propose rewording the title as follows: “*Options of Statistical Approaches to Stability data Analysis*”.

In addition, we suggest that recommendations provided in this appendix be moved to the text of the guidance.

### **B.5 Data Analysis for Matrixing Design studies**

*Page 12*

Considering the complexity of matrixing design, this section would need to be more specific and detailed.

On behalf of Aventis Pharmaceuticals Inc. we appreciate the opportunity to comment on Q1E Evaluation of Stability Data and thank you for your consideration.

Sincerely,

A handwritten signature in cursive script that reads "Steve Caffé for".

Steve Caffé, M.D.

*Vice President, Head US Regulatory Affairs*

biological products. The draft guidance defines the means for industry-to-agency transfer of regulatory information that will facilitate the creation, review, life cycle management, and archiving of the electronic submission. The draft guidance is intended to assist industry in transferring their marketing applications for human drug and biological products to a regulatory authority. The second draft guidance includes the following changes:

- The language in the guidance has been edited to improve clarity.
- The maximum length of a file name has been increased from 32 characters to 64 characters.
- Throughout the guidance, references to Common Technical Document (CTD) sections have been updated to reflect the current CTD.
- Appendix 4 has been reorganized.
- The examples in Appendix 6 have been updated.
- The Glossary of Terms has been completed.

This draft guidance, when finalized, will represent the agency's current thinking on "Electronic Common Technical Document Specification." 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 statutes and regulations.

## II. Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments on the draft guidance by August 1, 2002. 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 guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

## III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: June 6, 2002.

**Margaret M. Dotzel,**

*Associate Commissioner for Policy*

[FR Doc. 02-15003 Filed 6-13-02; 8:45 am]

BILLING CODE 4160-01-S

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 02D-0237]

#### International Conference on Harmonisation; Draft Guidance on Q1E Evaluation of Stability Data; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled "Q1E Evaluation of Stability Data." The draft guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This draft guidance is an annex to an ICH guidance entitled "Q1A(R) Stability Testing of New Drug Substances and Products." The draft guidance is intended to provide guidance on how to use stability data, generated in accordance with the principles outlined in Q1A(R), to propose a retest period for the drug substance and a shelf life for the drug product.

**DATES:** Submit written or electronic comments on the draft guidance by August 1, 2002.

**ADDRESSES:** Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-3844, FAX 888-CBERFAX. Send two self-addressed adhesive labels to assist the office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

#### FOR FURTHER INFORMATION CONTACT:

*Regarding the guidance:* Chi-wan Chen, Center for Drug Evaluation and Research (HFD-830), Food and Drug Administration, 5600 Fishers Lane,

Rockville, MD 20857, 301-827-2001; or Andrew Shrake, Center for Biologics Evaluation and Research (HFM-345), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1148, 301-402-4635.

*Regarding the ICH:* Janet J. Showalter, Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0864.

#### SUPPLEMENTARY INFORMATION:

##### I. Background

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, Labour, 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, Health Canada's Health Products and Food Branch, and the European Free Trade Area.

In accordance with FDA's good guidance practices (GGPs) regulation (21 CFR 10.115), this document is being

called a guidance, rather than a guideline.

To facilitate the process of making ICH guidances available to the public, the agency has changed its procedure for publishing ICH guidances. Beginning April 2000, we no longer include the text of ICH guidances in the **Federal Register**. Instead, we publish a notice in the **Federal Register** announcing the availability of an ICH guidance. The ICH guidance will be placed in the docket and can be obtained through regular agency sources (see **ADDRESSES**). Draft guidances are left in the original ICH format. The final guidance is reformatted to conform to the GGP style before publication.

In February 2002, the ICH Steering Committee agreed that a draft guidance entitled "Q1E Evaluation of Stability Data" should be made available for public comment. The draft 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.

This draft guidance is an annex to an ICH guidance entitled "Q1A(R) Stability Testing of New Drug Substances and Products" (66 FR 56332, November 7, 2001). The draft guidance is intended to provide guidance on how to use stability data, generated in accordance with the principles outlined in Q1A(R), to propose a retest period for the drug substance and a shelf life for the drug product.

The guidance on the evaluation and statistical analysis of stability data provided in Q1A(R) is brief in nature and limited in scope. Although Q1A(R) states that regression analysis is an acceptable approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25, it includes few details on these topics. In addition, Q1A(R) does not cover situations where multiple factors are involved in a full- or reduced-design study. This draft guidance provides a clear explanation of expectations when proposing a retest period or shelf life and storage conditions based on the evaluation of stability data for both quantitative and qualitative test attributes. It outlines recommendations for establishing a retest period or shelf life based on stability data from single-factor or multifactor and full- or reduced-design studies. The draft guidance further describes when and how limited extrapolation can be undertaken to propose a retest period or shelf life beyond the observed range of data from

the long-term storage condition. When finalized, the Q1E guidance will supersede the "Evaluation" sections of Q1A(R).

This draft guidance, when finalized, will represent the agency's current thinking on stability data evaluation. 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 statutes and regulations.

## II. Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written comments on the draft guidance by August 1, 2002. 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 guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

## III. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/ohrms/dockets/default.htm>, <http://www.fda.gov/cder/guidance/index.htm>, or <http://www.fda.gov/cber/publications.htm>.

Dated: June 6, 2002.

**Margaret M. Dotzel,**

*Associate Commissioner for Policy.*

[FR Doc. 02-15001 Filed 6-13-02; 8:45 am]

**BILLING CODE 4160-01-S**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 02D-0232]

#### International Conference on Harmonisation; Draft Guidance on S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled "S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human

Pharmaceuticals." The draft 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 guidance provides general principles and information on currently available nonclinical methodologies to identify the potential risk of QT interval prolongation by a pharmaceutical and recommends study types and timing of studies in relation to clinical development of a pharmaceutical. The draft guidance is intended to protect clinical trial participants and patients receiving marketed products from delayed repolarization-associated ventricular tachycardia, torsade de pointes, and lethal arrhythmias resulting from administration of pharmaceuticals.

**DATES:** Submit written or electronic comments on the draft guidance by August 1, 2002.

**ADDRESSES:** Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or the Office of Communication, Training and Manufacturers Assistance (HFM-40), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-3844, FAX: 888-CBERFAX. Send two self-addressed adhesive labels to assist the office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

#### FOR FURTHER INFORMATION CONTACT:

*Regarding the guidance:* John Koerner, Center for Drug Evaluation and Research (HFD-110), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5338, or David Green, Center for Biologics Evaluation and Research (HFM-579), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

*Regarding the ICH:* Janet J. Showalter, Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-

**Fournier, Elisabeth PH/US**

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**From:** Jullien, Isabelle PH/FR  
**Sent:** Monday, March 04, 2002 4:00 AM  
**To:** GRAMS CMC-EU/FR; BRW RI 2 Quality; BRW RI 3 Gen EU; BRW RI Comments; RA - Europe1:European Union  
**Cc:** Melcion, Celine PH/FR; Boyd, James PH/US; Aktogu, Nurgun PH/FR; Chapart, Brigitte PH/FR; Le Dantec, Erwan PH/FR; Brownlie, Fiona PH/DE  
**Subject:** Commenting # 20 Request for Comments: EMEA, ICH Guidance on Evaluation of Stability Data - Draft 28 Feb 2002

Dear All,

The European Agency for the Evaluation of Medicinal products (EMA), EU published (27 February 2002) the ICH Note for Guidance (ICH Q1E) on the evaluation of stability data (CPMP/ICH/420/02). **The document provides recommendations on how to use stability data generated in accordance with the principles detailed in guidelines ICH Q1A(R)** (Harmonised Tripartite guideline on Stability Testing of New Drug Substances and Products). The guidance is released for consultation only. The deadline for comments is August 2002. Further information can be obtained by following the links below

**For this topic Nurgun Aktogu will nominate the GRAMS EU group leader.**

**Regulatory Intelligence isabelle.jullien@aventis.com, needs to receive GLOBAL consolidated comments before 01 July 2002**

Internal Deadline: 01-Jul-2002  
Contact: Isabelle.Jullien@aventis.com

Links:  
[EMA, ICH guidance- ICH Q1E](#)

Regards,  
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*To the best of our knowledge, the above information is accurate, complete and up-to-date. If any reader of this document has additional information or is not in agreement with the contents please contact Global Regulatory Intelligence.*

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT CONSENSUS GUIDELINE

EVALUATION OF STABILITY DATA

Released for Consultation  
at *Step 2* of the ICH Process  
on 7 February 2002  
by the ICH Steering Committee

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.*

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. 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 statutes and regulations.

# EVALUATION OF STABILITY DATA

## Draft ICH Consensus Guideline

Released for Consultation, 7 February 2002, at *Step 2* of the ICH Process

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# EVALUATION OF STABILITY DATA

## 1. INTRODUCTION

### 1.1 Objectives of the Guidelines

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline Q1A(R) on "Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) to propose a retest period or shelf life. This guideline describes when and how limited extrapolation can be undertaken to propose a retest period for a drug substance or shelf life for a drug product beyond the observed range of data from the long-term storage condition.

### 1.2 Background

The guidance on the evaluation and statistical analysis of stability data provided in the parent guideline is brief in nature and limited in scope. Although the parent guideline states that regression analysis is an acceptable approach to analyzing quantitative stability data for retest period or shelf life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25, it includes few details. In addition, the parent guideline does not cover situations where multiple factors are involved in a full or reduced-design study. When this guideline reaches *Step 4*, the Evaluation sections of the parent guideline will become redundant and will therefore be removed.

### 1.3 Scope of the Guideline

This guideline, an annex to the parent guideline, is intended to provide a clear explanation of expectations when proposing a retest period or shelf life and storage conditions based on the evaluation of stability data for both quantitative and qualitative test attributes. This guideline outlines recommendations for establishing a retest period or shelf life based on stability data from single or multi-factor and full or reduced-design studies. ICH Q6A and Q6B provide guidance on the setting and justification of acceptance criteria.

## 2. GUIDELINES

### 2.1 General Principles

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances.

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms). Where appropriate, attention should be paid to reviewing the adequacy of the mass balance. Factors that can cause an apparent lack of mass balance should be considered, for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures. The degree of

variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

The recommendations in this guideline on statistical approaches are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. However, statistical analysis can be useful in the extrapolation of retest periods or shelf lives in certain situations and may be called for to verify the retest periods or shelf lives in other cases.

The basic concepts of stability data evaluation are the same for single- versus multi-factor studies and for full- versus reduced- design studies. Data evaluation from the formal stability studies, and as appropriate, supporting data should be used to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately and an overall assessment made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute.

A flow diagram is provided in Appendix A and some statistical approaches are provided in Appendix B on how to analyze and evaluate long-term stability data for appropriate quantitative test attributes from a study with a multi-factor full or reduced design. The statistical method used for data analysis should consider the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. Appendix B also provides information on how to use regression analysis for retest period or shelf life estimation and examples of statistical procedures to determine poolability of data from different batches or other factors. Additional guidance is provided by the list of references; however, the examples and references do not attempt to cover all other applicable statistical approaches.

In general, certain quantitative chemical attributes (e.g., assay, degradation products, preservative content) for a drug substance or product can be assumed to follow zero-order kinetics during long-term storage. Data for these attributes are therefore amenable to linear regression and poolability testing, as illustrated in Appendix B. Qualitative attributes are not amenable to statistical analysis, and microbiological attributes and certain quantitative attributes (e.g., pH, dissolution) are generally not amenable to the type of statistical analysis described in Appendix B.

## **2.2 Data Presentation**

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of those data should be included in the application. If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included.

## **2.3 Extrapolation**

Limited extrapolation to extend the retest period or shelf life beyond the observed range of available long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Any extrapolation should take into consideration the possible worst-case situation at the time of batch release.

Extrapolation is the practice of using a known data set to infer information about future data sets. An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the observed range of available long-term data. Hence, the use of extrapolation should be justified in terms of, for example, what is

known about the mechanisms of degradation, the goodness of fit of any mathematical model, and the existence of relevant supporting data.

The correctness of the assumed change pattern is crucial if extrapolation beyond the available long-term data is contemplated. For example, when estimating a regression line or curve within the available data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is available beyond the length of observed data. Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the extrapolated retest period or shelf life.

## **2.4 Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for "Room Temperature" Storage**

A systematic evaluation of the data from formal stability studies should be performed as illustrated in this section. In general, stability data for each attribute should be assessed sequentially, beginning with significant change, if any, at the accelerated condition and, if appropriate, the intermediate condition, and progressing through the trends and variability of long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the observed length of long-term data can be appropriate.

### **2.4.1 No Significant Change at Accelerated Condition**

Where no significant change occurs at the accelerated condition, the retest period or shelf life setting would depend on the nature of the long-term and accelerated data.

#### *2.4.1.1 Long-term and accelerated data showing little or no change over time and little or no variability*

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it may be apparent that the drug substance or product will remain well within its acceptance criterion for that attribute during the proposed retest period or shelf life. Under these circumstances, it is normally considered unnecessary to go through a statistical analysis, but justification for the omission should be provided. Justification can include a discussion of the mechanisms of degradation or lack of degradation, relevance of the accelerated data, mass balance, and/or other supporting data as defined in the parent guideline.

Extrapolation of the retest period or shelf life beyond the length of available long-term data can be proposed. A proposed retest period or shelf life up to twice the length of available long-term data can be proposed, but it should not exceed the length of available long-term data by more than 12 months.

#### *2.4.1.2 Long-term or accelerated data showing change over time and variability*

If the long-term or accelerated data for an attribute show change over time and/or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are considerable differences in stability observed among batches or other factors (e.g., container size and/or fill, strength) or factor combinations (e.g., strength-by-container size and/or fill), the proposed retest period or shelf life should be based on the shortest period supported by the worst batch, factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength),

different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such a difference on the product. Extrapolation beyond the length of available long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

- *Data not amenable to statistical analysis (for qualitative attributes or certain quantitative attributes)*

When relevant supporting data are provided, a retest period or shelf life up to one and a half times the length of available long-term data can be proposed, but should not exceed the length of available long-term data by more than 6 months. Relevant supporting data include satisfactory long-term data from development batches that are made with a closely related formulation to, manufactured on a smaller scale than, or packaged in a container closure system similar to that of the primary stability batches.

- *Data amenable to statistical analysis*

If a statistical analysis is not performed, the extent of extrapolation should be the same as above (i.e., when relevant supporting data are provided, a retest period or shelf life up to one-and-a-half times the length of available long-term data can be proposed, but should not exceed the length of available long-term data by more than 6 months.) However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice the length of available long-term data, when supported by the statistical analysis and supporting data, although this proposed retest period or shelf life should not exceed the length of available long-term data by more than 12 months.

#### **2.4.2 Significant Change at Accelerated Condition**

Where significant change\* occurs at the accelerated condition, the retest period or shelf life setting would depend on the outcome of stability testing at the intermediate condition, as well as long-term testing.

\*The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change (potential interaction effects should also be considered in establishing that there is no other significant change): (1) softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated; and (2) failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if it can be unequivocally attributed to cross-linking. However, phase separation of semisolid dosage forms at the accelerated condition could call for testing at the intermediate condition.

##### **2.4.2.1 No significant change at intermediate condition**

If there is no significant change at the intermediate condition, extrapolation beyond the length of available long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

- *Data not amenable to statistical analysis*

Based on an attribute that is not amenable to statistical analysis, a retest period or shelf life can be proposed, when relevant supporting data are provided, but the proposed retest period or shelf life should not exceed the length of available long-term data by more than 3 months.

- *Data amenable to statistical analysis*

If the long-term data for an attribute are amenable to statistical analysis but such an analysis is not performed, the extent of extrapolation would be the same as above. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to one-and-half times the length of available long-term data, when supported by the statistical analysis and relevant supporting data, but not exceeding the length of available long-term data by more than 6 months.

#### *2.4.2.2 Significant change at intermediate condition*

Where significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the extent of available long-term data. In addition, a shorter retest period or shelf life could be called for. If the long-term data show variability, verification of the retest period or shelf life by statistical analysis can be appropriate

## **2.5 Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products Intended for Storage Below "Room Temperature"**

### ***2.5.1 Drug Substances or Products Intended for Refrigerated Storage***

Data from products intended to be stored in a refrigerator should be assessed according to the same principles described throughout this document for the general case pertaining to products intended for "room temperature" storage, except where explicitly noted in the section below. A decision tree is provided in Appendix A as an aid to the guidance below.

#### *2.5.1.1 No significant change at accelerated condition for products intended for refrigerated storage*

Where no significant change occurs at the accelerated condition, extrapolation of retest period or shelf life beyond the length of available long-term data can be proposed. The proposed retest period or shelf life can be up to one and a half times the length of available long-term data, but should not exceed the length of available long-term data by more than 6 months.

#### *2.5.1.2 Significant change at accelerated condition for products intended for refrigerated storage*

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real time data available at the long-term storage condition. No extrapolation can be considered.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the real time data available at the long-term storage condition. No extrapolation should be performed. In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance or product for a period shorter than 3 months.

### ***2.5.2 Drug Substances or Products Intended for Storage in a Freezer***

For drug substances and products intended for storage in a freezer, the retest period or shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances or

products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g.,  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  or  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition (e.g., during shipping or handling).

### **2.5.3 Drug Substances or Products Intended for Storage Below $-20^{\circ}\text{C}$**

For drug substances and products intended for storage below  $-20^{\circ}\text{C}$ , the retest period or shelf life should be based on the real time data obtained at the proposed long-term storage condition and should be assessed on a case by case basis.

## **2.6 General Statistical Approaches**

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. This same method could also be applied to commitment batches to verify or extend the originally approved retest period or shelf life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear or non-linear function on an arithmetic or logarithmic scale. Sometimes a non-linear regression can be expected to better reflect the true relationship.

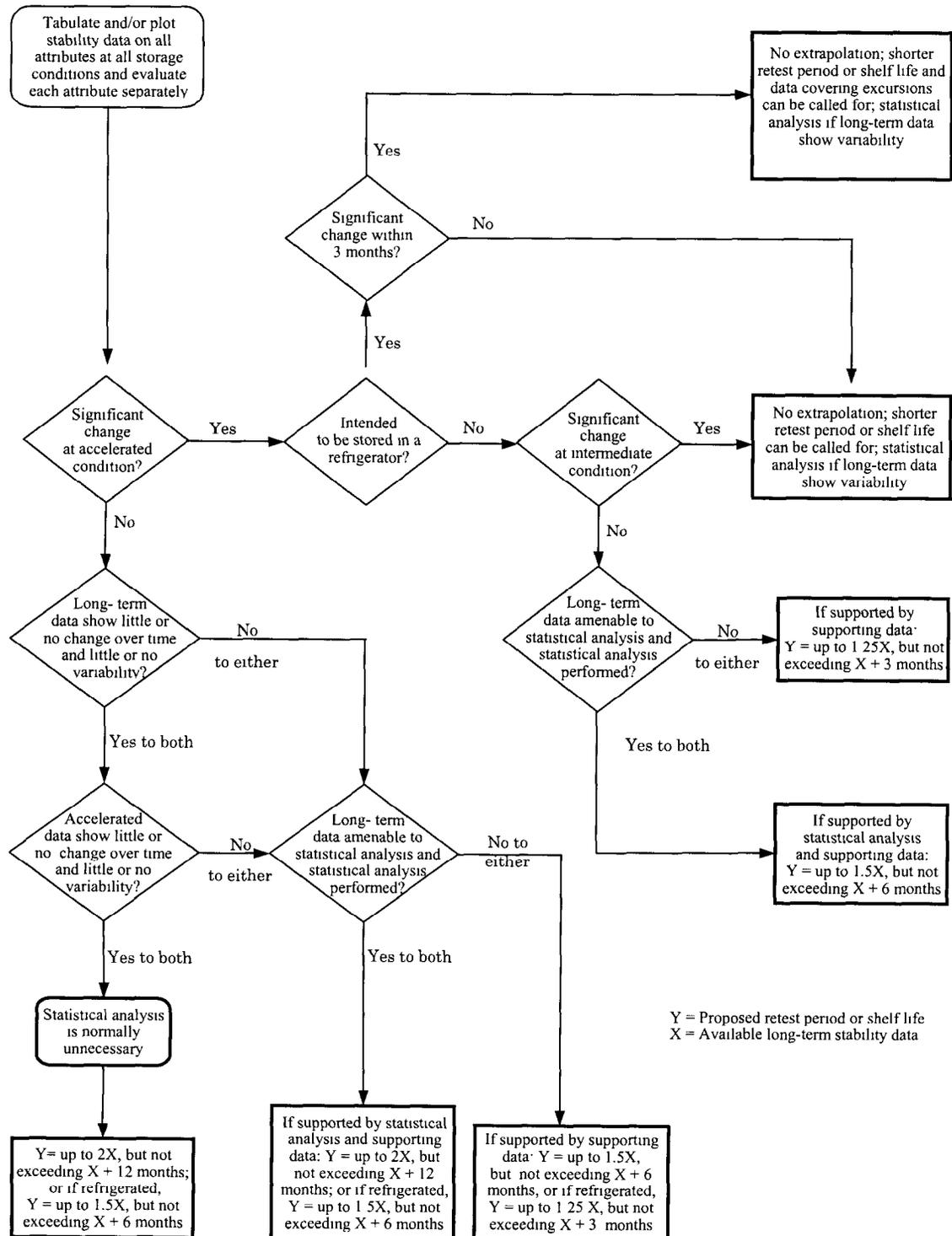
An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute by determining the earliest time at which the 95 percent confidence limit for the mean around the regression curve intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95 percent confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one sided 95 percent confidence limit should be compared to the criterion. For an attribute which can either increase or decrease, or whose direction of change is not known, two-sided 95 percent confidence limits should be calculated and compared to the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when combined after an appropriate statistical test. Examples of statistical approaches to the analysis of stability data from full, bracketing, and matrixing designs are included in Appendix B. References to current literature sources can be found in Appendix B.6.

3. APPENDICES

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substances or Products (excluding frozen products)



## **Appendix B: Examples of Statistical Approaches to Stability Data Analysis**

Linear regression, poolability tests, and statistical modeling, described below, are examples of statistical methods and procedures that can be used in the analysis of stability data for a quantitative attribute that is amenable to linear regression and for which there is a proposed acceptance criterion.

### **B.1. Data Analysis for a Single Batch**

In certain cases, the relationship between an attribute and time is assumed to be linear.<sup>1</sup> Figure 1a shows the regression line for assay of a product with upper and lower acceptance criteria of 105 percent and 95 percent of label claim, respectively, with 12 months of long-term data. In this example, two sided 95 percent confidence limits for the mean are applied because it is not known ahead of time whether the assay would increase or decrease with time. The lower 95 percent confidence limit intersects the lower acceptance criterion at 30 months. Therefore, a proposed shelf life of up to 24 months can be supported by the statistical analysis as long as the recommendations in Sections 2.4 and 2.5 are followed.

When data for an attribute with only an upper or a lower acceptance criterion are analyzed, the corresponding one-sided 95 percent confidence limit for the regression line is recommended. Figure 1b shows the regression line for a degradation product with 12 months of long-term data, where the acceptance criterion is not more than 1.4 percent. The one-sided 95 percent confidence limit for the mean intersects the acceptance criterion at 31 months. Therefore, a proposed retest period or shelf life of 24 months can be supported by the statistical analysis of the degradation data as long as the recommendations in Sections 2.4 and 2.5 are followed.

If the above approach is used, the values of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within acceptance criteria through the end of the retest period or shelf life at a confidence level of 95 percent. If, however, the acceptance criterion for the quantitative attribute calls for individual values, confidence limits for the individual values should be used (e.g., content uniformity for some complex dosage forms).

The approach described above can be used to estimate the retest period or shelf life for a single batch, individual batches or multiple batches when combined after appropriate statistical tests described in Sections B.2 through B.5.

### **B.2. Data Analysis for One-Factor, Full-Design Studies**

For a drug substance or for a drug product available in a single strength and a single container size and/or fill, the retest period or shelf life is generally estimated based on the stability data from a minimum of three batches. Two approaches can be considered when analyzing such data. The objective of the first approach, testing for poolability, is to determine whether the data from different batches can be combined for an overall estimate of a single shelf life. The objective of the second approach is to determine whether the data from all batches support the proposed shelf life.

#### **B.2.1 Testing for Poolability of Batches**

##### ***B.2.1.1 Analysis of Covariance***

Before pooling the data from several batches to estimate a retest period or shelf life, a preliminary statistical test should be performed to determine whether the regression lines from different batches have a common slope and a common time-zero intercept. Analysis of covariance (ANCOVA) can be employed, where time is considered the covariate, to test the differences in slopes and intercepts of the regression lines among

batches. Each of these tests should be conducted using a significance level of 0.25 to compensate for the expected low power of the design due to the relatively limited sample size in a formal stability study.

If the test rejects the hypothesis of equality of slopes (i.e., there is a significant difference in slopes among batches), it is considered inappropriate to combine the data from all batches. The retest periods or shelf lives for individual batches in the stability study can then be estimated by applying the approach as described in B.1 using individual intercepts and individual slopes and the pooled mean square error calculated from all data. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the test rejects the hypothesis of equality of intercepts but fails to reject that the slopes are equal, (i.e., there is a significant difference in intercepts but no significant difference in slopes among the batches), the data can be combined for the purpose of estimating the common slope. The retest periods or shelf lives for individual batches in the stability study should then be estimated by applying the approach as described in B.1, using the common slope and individual intercepts. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the tests for equality of slopes and equality of intercepts do not result in rejection at a level of significance of 0.25 (i.e., there is no significant difference in slope and intercepts among the batches), the data from all batches can be combined. A single shelf life can be estimated from the combined data by using the approach as described in B.1 and applied to all batches. The estimated shelf life from the combined data is usually longer than that from individual batches because the confidence limit(s) about the regression line will become narrower as the amount of data increases when batches are combined.

The above pooling tests should be performed in a proper order, such that the slope terms are tested before the intercept terms. The most reduced model (i.e., individual slopes, common slope with individual intercepts, or common slope with common intercept, as appropriate) can be selected for shelf life estimation.

#### ***B.2.1.2 Other Methods***

Statistical procedures<sup>2-6</sup> other than those described above can be used in retest period or shelf life estimation. For example, if it is possible to decide in advance the acceptable difference in slope or in mean shelf life among batches, an appropriate procedure for assessing the equivalence in slope or in mean shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, and justified and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate the appropriate statistical properties of the alternative procedure selected.<sup>7</sup>

#### **B.2.2 Evaluating Whether all Batches Support Proposed Retest Period or Shelf Life**

The objective of this approach is to evaluate whether some of the batches have retest periods or shelf lives shorter than those proposed. Retest periods or shelf lives for individual batches should first be estimated using the procedure described in B.1 with individual intercepts, individual slopes, and the pooled mean square error calculated from all data. If each batch has an estimated retest period or shelf life longer than that proposed, the proposed retest period or shelf life will generally be considered appropriate, as long as the guidance for extrapolation in Section 2.4-2.5 is followed. There is generally no need to perform poolability tests or identify the most reduced

model. If, however, one or more of the estimated retest periods or shelf lives are shorter than that proposed, poolability tests can be performed to determine whether the batches can be combined to estimate a longer retest period or shelf life.

Alternatively, this approach can be taken during the pooling process described in B.2.1.1. If the regression lines for the batches are found to have a common slope and the estimated shelf lives based on the common slope and individual intercepts are all longer than the proposed shelf life, there is generally no need to continue to test the intercepts for poolability.

### **B.3.Data Analysis for Multi-Factor, Full-Design Studies**

The stability of the drug product could differ to a certain degree among different factor combinations in a multi-factor, full design study. Two approaches can be considered when analyzing such data. The objective of the first approach, testing for poolability, is to determine whether the data from different factor combinations can be combined for an overall estimate of a single retest period or shelf life. The objective of the second approach is to determine whether the data from all factor combinations support the proposed retest period or shelf life.

#### **B.3.1 Testing for Poolability**

The stability data from different combinations of factors should not be combined unless supported by statistical tests for poolability.

##### ***B.3.1.1 Testing for Poolability of Batch Factor Only***

If each factor combination is considered separately, the stability data can be tested for poolability of batches only, and the retest period or shelf life for each non-batch factor combination can be estimated separately by applying the procedure described in B.2. For example, for a drug product available in two strengths and four container sizes, eight sets of data from the 2x4 strength-size combinations will be analyzed and eight separate shelf lives should be estimated accordingly. If a single shelf life is desired, the shortest estimated shelf life among all factor combinations should become the shelf life for the product. However, this approach does not take advantage of the available data from all factor combinations, thus generally resulting in shorter shelf lives than does the approach in B.3.1.2.

##### ***B.3.1.2 Testing for Poolability of all Factors and Factor Combinations***

If the stability data are tested for poolability of all factors and factor combinations and the results show that the data can be combined, a single retest period or shelf life longer than that estimated based on individual factor combinations is generally obtainable. The retest period or shelf life is longer because the confidence limit(s) about the estimated regression line will become narrower as the amount of data increases when batches, strengths, container sizes and/or fills, etc. are combined.

###### ***B.3.1.2.1 Analysis of Covariance***

Analysis of covariance can be employed to test the difference in slope and intercept of the regression lines among factors and factor combinations.<sup>7, 8</sup> The purpose of the procedure is to determine whether data from multiple factor combinations can be combined for the estimation of a single retest period or shelf life.

The full statistical model should include the intercept and slope terms of all main effects and interaction effects, and a term reflecting the random error of measurement. If it can be justified that the higher order interactions are very small, there is generally no need to include these terms in the model. In cases where the

analytical results at the initial time point are obtained from the finished dosage form prior to its packaging, the container intercept term can be excluded from the full model because the results are common among the different container sizes and/or fills.

The test for poolability should be specified to determine whether there are statistically significant differences among factors and factor combinations. Generally, the pooling test should be performed in a proper order, such that the slope terms are tested before the intercept terms and the interaction effects are tested before the main effects. For example, the test can start with the slope and then the intercept terms of the highest order interaction, and proceed to the slope and then the intercept terms of the simple main effects. The most reduced model, obtained when all remaining terms are found to be statistically significant, can be used to estimate the shelf lives.

All tests should be conducted using appropriate levels of significance. It is recommended that a significant level of 0.25 be used for any terms involving batch and a significant level of 0.05 be used for terms not involving batch. If the tests for poolability show that the data from different factor combinations can be combined, the shelf life can be estimated according to the procedure described in B.1, using the combined data.

If the tests for poolability show that the data from certain factors or factor combinations should not be combined, either of two alternatives can be applied: (1) a separate shelf life can be estimated for each level of the factors and of the factor combinations remaining in the model; or (2) a single shelf-life can be estimated based on the shortest estimated shelf-life among all levels of factors and of the factor combinations remaining in the model.

#### *B.3.1.2.2 Other Methods*

Alternative statistical procedures<sup>2-6</sup> to those described above can be applied. For example, an appropriate procedure for assessing the equivalence in slope or in mean shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, properly justified, and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate the appropriate statistical properties of the alternative procedure selected.<sup>7</sup>

### **B.3.2 Evaluating Whether All Factor Combinations Support Proposed Retest Period or Shelf Life**

The objective of this approach is to evaluate whether some of the factor combinations have shelf lives shorter than the proposed shelf life. The statistical model should be constructed as described in B.3.1.2.1, and the shelf life can be estimated for each level of each factor and factor combination. If all estimated shelf lives are longer than the proposed shelf life, no further model building is considered necessary and the proposed shelf life will generally be considered appropriate as long as the guidance in Sections 2.4 and 2.5 is followed. If one or more of the estimated shelf lives fall short of the proposed shelf life, model building as described in B.3.1.2.1 can be employed. However, it is generally considered unnecessary to identify the final model before evaluating whether the data support the proposed shelf life. Shelf lives can be estimated at each stage, and if all shelf lives are longer than the proposed, further modeling is considered unnecessary. This approach can simplify the data analysis of a complicated multi-factor stability study compared to that described in B.3.1.2.1.

#### **B.4. Data Analysis For Bracketing Design Studies**

The same statistical procedures as described in B.3 can be applied to the analysis of stability data obtained from a bracketing design. For example, for a drug product available in three strengths (S1, S2, and S3) and three container sizes (P1, P2, and P3) and studied according to a bracketing design where only the two extremes of the container sizes (P1 and P3) are tested, six sets of data from the 3x2 strength-size combinations will be obtained. The data can be analyzed separately for each of the six combinations for shelf life estimation according to B.3.1.1, or tested for poolability prior to shelf life estimation according to B.3.1.2.

The bracketing design assumes that the stability of the intermediate strengths or sizes is represented by the stability at the extremes. If the statistical analysis indicates that the stability of the extreme strengths or sizes is different, the intermediate strengths or sizes should be considered no more stable than the least stable extreme. For example, if P1 from the above bracketing design is found to be less stable than P3, the shelf life for P2 should not exceed that for P1. No interpolation between P1 and P3 should be considered.

#### **B.5. Data Analysis For Matrixing Design Studies**

A matrixing design has only a fraction of the total number of samples tested at any specified time point; therefore, it is important to ascertain that all factors and factor-by-factor interactions that can have an impact on shelf life estimation have been appropriately tested. For a meaningful interpretation of the study results and shelf life estimation, certain assumptions should be made and justified. For instance, the assumption that the stability of the samples tested represents the stability of all samples should be valid. In addition, if the design is not balanced, some factors or factor-by-factor interactions could not be estimable. Furthermore, for different levels of factor combinations to be poolable, it might have to be assumed that the higher order factor-by-factor interactions are negligible. Because it is impossible to statistically test the assumption that the higher order terms are negligible, this type of matrixing design should be used only when it is reasonable to assume that these interactions are indeed very small, based on supporting data.

The statistical procedure described in B.3 can be applied to the analysis of stability data obtained from a matrixing design. The same procedure for pooling the data from different batches, strengths, and/or container sizes and/or fill should be applied. However, since not every combination of factors will be tested at all time points, the statistical analysis should clearly identify the procedure and assumptions used. For instance, the assumptions underlying the model in which interaction terms are negligible should be stated. If a preliminary test is performed for the purpose of eliminating factor combinations from the model, the procedure used should be provided and justified. The final model on which the estimation of shelf life will be based should be stated. The estimation of shelf life should be performed for each of the terms remaining in the model. The use of a matrixing design can result in a shorter estimated shelf life than use of a full design.

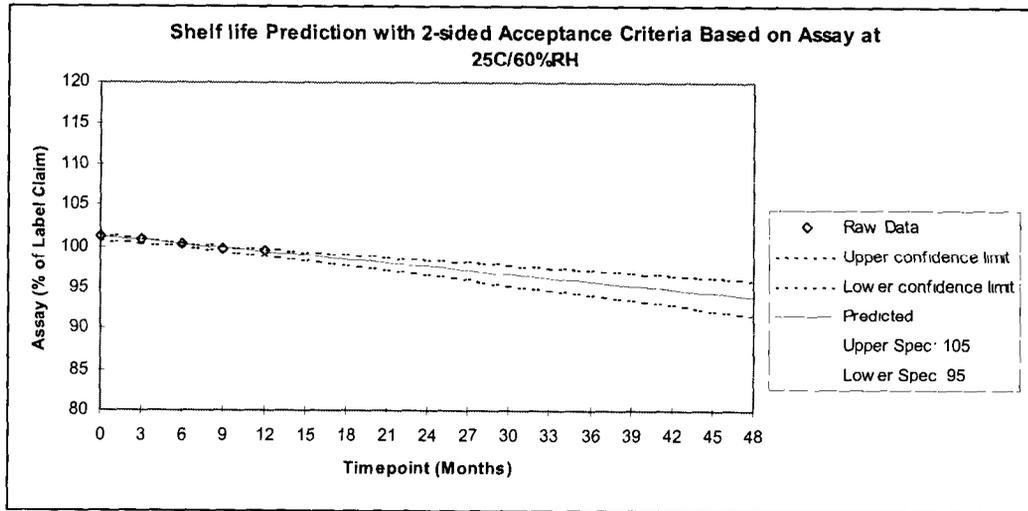
Where bracketing and matrixing are combined in one design, the statistical procedure described in B.3 can be applied.

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B.7 Figures

1.a.



1.b.

