Guidance for Industry

ANDAs: Stability Testing of Drug Substances and Products

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2014
Generics

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides answers to questions from the public comments we received on the draft guidance for industry on *ANDAs: Stability Testing of Drug Substances and Products*[2] (FDA stability guidance) that published in the Federal Register of September 25, 2012. The final guidance for industry of the same title published in the Federal Register of June 20, 2013. Comments received on the draft of this guidance published in the Federal Register of August 27, 2013 have also been incorporated. General issues; drug master files (DMFs); drug product manufacturing and packaging; and stability studies are discussed in this guidance and are intended to clarify the stability testing data recommendations for abbreviated new drug applications (ANDAs). In this document, the terms drug substance and active pharmaceutical ingredient (API) are used interchangeably.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. General

Q1: What is the scope of and implementation date for the FDA stability guidance?

A1: The FDA stability guidance covers all new ANDAs under the Federal Food, Drug, and Cosmetic Act, section 505 (j), and DMFs (Type II for drug

[1] This guidance has been prepared by the Office of Generic Drugs and Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

substances that support the ANDAs). It does not apply to postapproval changes.

The implementation date is June 20, 2014.

Q2: How will this guidance affect the President's Emergency Plan for AIDS Relief (PEPFAR) and positron emission tomography (PET) ANDAs?

A2: For chemistry, manufacturing, and controls (CMC) information, PEPFAR ANDAs should follow the guidance for industry on *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV.*[3]

For PET ANDAs, the Agency recommends a minimum of three batches at or near the upper end of the proposed radio-concentration. If different synthesizers (methods of synthesis) are used, three batches from each method of synthesis at or near the upper end of the proposed radio-concentration are recommended. Batches do not have to be made in the same facility. For any additional manufacturing facilities, applicants should provide stability data on at least one batch at or near the upper end of the proposed radio-concentration from each facility, although bracketing approaches may be submitted for review. For additional information, the Agency has published a guidance for industry on *FDA Oversight of PET Products, Questions and Answers*.[4]

Q3(i): Can an ANDA be submitted with 6 months of accelerated stability and 6 months of long-term stability data?

A3(i): Yes. An ANDA applicant should submit 6 months of accelerated stability data and 6 months of long-term stability data at the time of submission. However, if 6 months of accelerated data show a significant change[5] or failure of any attribute, the applicant should also submit 6 months of intermediate data at the time of submission.

Q3(ii): When do intermediate stability studies need to be initiated in the event of failure at accelerated condition?

A3(ii): An ANDA applicant should start accelerated, intermediate, and long-term stability studies at the same time so the data are available at the time of submission if the accelerated stability study fails.

[3] See footnote 2.
[4] Ibid.
[5] See the International Conference on Harmonisation (ICH) guidance to industry on *Q1A(R2) Stability Testing of New Drug Substances and Products*, section 2.2.7.1.

Q3(iii): If one among the three batches in accelerated conditions shows a significant change, what should be done?

A3(iii): If accelerated data show a significant change or failure of any attribute in one or more batches, an applicant should submit intermediate data for all three batches. In addition, the submission should contain a failure analysis (i.e., discussion concerning the observed failure(s)).

Q4: Can stability bracketing and/or matrixing be used to determine the packaging configurations to be placed on stability for an original ANDA without prior approval from the Office of Generic Drugs (OGD)?

A4: Yes. You should follow the International Conference on Harmonisation (ICH) guidance for industry on *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products*[6] and its example tables.

Q5(i): If an application that qualifies for the Generic Drug User Fee Act (GDUFA) 10-month review is filed with 6 months of accelerated and 6 months of long-term data, and there are no blocking patents or exclusivities, will 24 months of shelf life be granted?

Q5(ii): During the review cycle, will the application need to be updated with 12 months of long-term data?

A5(i,ii): FDA will grant a shelf life period of two times the available long-term data at the time of approval (up to 24 months) following the recommendation of the ICH *Q1E Evaluation of Stability Data* (ICH Q1E) guidance,[7] provided the submitted data are satisfactory, and data evaluation and appropriate commitments are provided in accordance with ICH Q1E. Please refer to the decision tree (Appendix A) in ICH Q1E. The ANDA should be updated with 12 months of long-term data during the review cycle.

Q6: Can only two lots of finished product at pilot scale batch size ever be considered sufficient to support the stability of an ANDA for simple dosage forms?

A6: According to the FDA stability guidance, the applicant should submit data from three pilot scale batches **or** should submit data from two pilot scale batches and one small scale batch. This applies to all dosage forms. If the size of the pilot scale batch does not follow ICH recommendations, the applicant should provide a justification. See also section C, question 20 for additional information regarding exceptions.

[6] See footnote 2.
[7] Ibid.

Q7: How is the proposed shelf life supposed to be calculated? Will 6 months of accelerated data equal 24 months at long-term?

A7: ICH Q1E principles will help in the calculation of shelf life. Data from the three ANDA submission batches (i.e., 6 months), accelerated data meeting all criteria (without significant change per ICH Q1A(R2)), and 12 months long-term data without variability will not need statistical evaluation, and with appropriate post approval stability commitments, can be used to support extrapolation to a 24 months shelf life.

If there is a significant change in the accelerated data, ICH Q1E, Appendix A, provides more details regarding when intermediate condition stability data are recommended.

Q8: Will the recommendation for 6 months accelerated data be met by providing 24 weeks of data as 12 weeks is typically accepted as equivalent to 3 months?

A8: No. FDA, following the recommendations of ICH stability guidances refers to timeframes in terms of months and not weeks.

Q9: When a patent is due to shortly expire and there are no approved ANDAs, can we file with 3 months stability data with a commitment to supply 6 months data when available?

A9: No. Data recommendations in the FDA stability guidance should be followed irrespective of patent status.

Q10: How long do the three pilot scale batches, submitted as a part of an ANDA, need to be stored before destruction?

A10: Sample storage times are discussed in 21 CFR 320.38 and 21 CFR 320.63 in connection with bioequivalence study samples. In general, ANDA submission batch samples should be stored for 1 year after approval of the ANDA, and samples of the drug product used for bioequivalence studies must be stored following the requirements listed in 21 CFR 320.38 and 21 CFR 320.63. In addition, the guidance for industry on *Handling and Retention of BA and BE Testing Samples*[8] may be helpful regarding the procedure for handling reserve samples from relevant bioavailability and bioequivalence studies. Additional information on sample quantities (for retention purposes) is discussed in 21 CFR 211.170 (a) and (b), Reserve Samples.

[8] See footnote 2.

B. Drug Master File

Q1: Please clarify the effect of the FDA stability guidance on Drug Master File (DMF) holders.

Q1(i): How many months of long-term and accelerated data are required when a "Completeness Assessment" is performed on the DMF? Also, what should the DMF stability section contain for a Completeness Assessment?

A1(i): To pass the Completeness Assessment, DMFs should include the stability protocol, commitments, and data demonstrating that stability studies have started. The initial and one additional time point for the accelerated studies and long-term studies are sufficient. If the DMF does not meet the recommendations under A1(ii) below at the time of the Completeness Assessment the DMF holder should amend the DMF with updated stability data to prepare for full scientific review.

Q1(ii): Are stability data from three current good manufacturing practice (CGMP) batches required to be filed in the DMF to support the API retest date? Also, how many months of long-term and accelerated data are required for pilot scale batches?

A1(ii): Yes. Per ICH Q1A(R2) data from formal stability studies should be provided on at least three primary batches[9] and the batches should be manufactured to a minimum of pilot scale[10] for the drug substance to be filed in the DMF. These batches should be made under CGMPs. The FDA stability guidance recommends 6 months of accelerated data and 6 months of long-term data for the pilot scale batches to be submitted for a full scientific review of the DMF. Additional long-term data for all three batches, as the data becomes available through the proposed retest period, should be submitted as an amendment.

Q2: Will submissions to DMFs be accepted based on stability data from production scale batches?

A2: Yes. Per ICH Q1A(R2), section II, A, 8, Stability Commitment (2.1.8), the submission is appropriate if satisfactory stability data from at least three production batches made under CGMP are filed in the DMF with 6 months of accelerated data and data for samples stored under long-term conditions that cover the proposed retest period.

Q3: Should executed batch records for the three batches be included in the DMF submission?

A3: One representative executed batch record will be sufficient.

[9] "Primary batch" is defined in ICH Q1A(R2) Glossary.
[10] See ICH Q1A(R2) Glossary.

C. Drug Product Manufacturing and Packaging

Q1: Can the split bulk solution filled into different fill volumes be considered discrete batches?

A1: To be consistent with ICH Q1A(R2), we recommend that discrete finished product batches be produced that represent different batches of bulk solution. Split filling one batch of bulk solution into different fill volume sizes would not constitute discrete batches.

Q2: Can you clarify the packaging recommendations for the submission batches for blow-fill-seal containers?

A2: Blow-fill-seal containers are not an exception from regular packaging and are usually packaged inside a secondary container or a carton. The secondary packaging should be included in all three batches. ICH Q1A(R2) addresses secondary packaging usefulness (see section II, B, 4, Drug Product Container Closure System (2.2.4)).

Q3: Should all three batches be stored in final proposed packaging?

A3: Yes. You should package all three batches in the container closure system proposed for marketing. ICH Q1A(R2) addresses this question (see section II, B, 4, Drug Product Container Closure System (2.2.4)).

Q4: What is the Agency's position on using different lots of APIs and/or packaging materials? How many API lots should be used in the manufacture of finished product lots used to support the ANDA?

A4: It is not necessary to use different lots of APIs or packaging material, except in cases where the packaging material could affect drug product performance and/or delivery. A minimum of two lots of the drug substance should be used to prepare the three primary batches of drug product.[11]

Q5: Should the small scale batches be packaged with commercial equipment? Also, is it acceptable to package using research equipment or by hand?

A5: Yes. Small scale batches should be packaged with commercial equipment, or the packaging equipment should be similar to that proposed for use prior to market distribution. No, it is not recommended to package small scale batches using research equipment or by hand. Please refer to ICH Q1A(R2) section II, B, 3, Selection of Batches (2.2.3) and the glossary definition for primary batches.

[11] For nasal aerosols and nasal sprays, you should use three different lots of drug substance.

Q6: What will the recommendation for secondary packaging be?

A6: We recommend following ICH Q1A(R2) section II, B, 4, Drug Product Container Closure System (2.2.4).

Q7: What are the recommendations for stability testing data of modified release dosage forms?

A7: Per ICH Q1A(R2) the applicant should provide data on three batches of all dosage forms including modified release dosage forms. ICH stability guidances do not distinguish among different dosage forms.

Q8: What are the recommendations for the submission of oral solutions, ophthalmic solutions, oral and ophthalmic suspensions, transdermal patches, ointments, creams, granules for reconstitution, and parenterals?

A8: The applicant should provide three discrete batches and 6 months of accelerated data and 6 months of long-term data at the time of submission for all dosage forms. Also, refer to other questions and corresponding answers that specifically discuss other dosage forms included in this document (e.g., questions Q7, Q13).

Q9: Are 6 months of stability data required on all three batches, or would one batch at 6 months and two lots at 3 months be acceptable?

A9: Following ICH stability guidances, 6 months accelerated stability data on all three submission batches should be provided.

Q10: Should the executed batch records for the three batches be included in the ANDA submission?

A10: Yes.

Q11: Does all relevant CMC batch information for the three stability batches need to be included in the application?

A11: Yes. When more than one lot of API or excipients is used, the corresponding section in Module 3 should contain appropriate CMC information.

Q12: If you are an applicant submitting an ANDA with two API sources, are you required to perform stability on three batches of drug product for each API source?

A12: If you propose to add additional sources of API for the same drug substance, you should provide the following CMC information:

- Comparison and justification of comparability (by the applicant) of the physico-chemical properties and impurities of the drug substance from each source.
- Appropriate stability data on three batches of drug product qualifying the first API source used in the bioequivalence (BE) studies as recommended by the FDA stability guidance.
- A single pilot scale batch of the drug product bio-strength(s) manufactured using the second or each of the other proposed API source(s) used to support the ANDA application, along with comparative dissolution data.
- Appropriate stability data (accelerated and long-term for 6 months at the time of filing) on the strength(s) manufactured for each API source. Appropriate stability data may in some cases include intermediate condition stability data.

Q13: What is meant by "small" scale? "Small" is not a defined word in ICH guidance. What are the packaging expectations from the small batch, as well as from the two pilot scale batches? Traditionally, ANDAs are submitted with 100,000 units for solid oral dosage forms. Is this still applicable?

A13: The interpretation of what constitutes a small scale batch for the purpose of filing ANDAs is further elaborated below for various dosage forms and their packaging recommendations. Unless specifically noted below, one primary batch should be fully packaged.

Oral dosage forms

(a) Tablets/Capsules (e.g., immediate release, extended release, chewable, orally disintegrating and delayed release tablets or capsules): Two of the three batches should be of at least 10 percent of the proposed production batch or 100,000 finished dosage units, whichever is greater (i.e., pilot scale batches). The third batch can be smaller than the 10 percent of the proposed production batch, but should not be less than 25 percent of the pilot scale batch. We recommend stability data be generated for the three ANDA submission batches in the proposed marketing container. A minimum of 100,000 units in all proposed presentations is recommended. Representative samples from all three batches must be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b) .

(b) Powders/Solutions/Suspensions: Two of the three batches should be at least 10 percent of the proposed maximum size commercial batch. The third batch can be smaller than 10 percent of the proposed commercial batch, but should not be less than 25 percent of the pilot scale batch. To capture variability introduced by packaging, the product from all the batches should be used in the packaging process. We recommend packaging representative

samples from all three batches of a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b) .

Parenterals

Solutions/Powders for Solutions (lyophilized cakes)/Suspensions/Sterile Topicals (Ophthalmic and Otic drug products): Two of the three batches should be at least (a) 10 percent of the proposed maximum size commercial batch (i.e., pilot scale size), (b) 50 L (per batch if the fill volume configurations per vial is larger than 2.0 mL), or (c) 30 L (per batch if the fill volume size is up to 2.0 mL) whichever is larger including packaging.[12] When multiple fill volume sizes are proposed by the applicant (e.g., 1 mL, 2 mL, and 3 mL), then 50 L per batch size is recommended. The third batch can be smaller than 10 percent of the proposed commercial batch, but should not be less than 25 percent of the pilot scale batch (with packaging).[13] To capture variability introduced by packaging, the product from each of multiple fill volume batches should be used in the packaging process. We recommend manufacturing all the batches to meet sterility requirements. Packaging requirements are also discussed in 21 CFR 211.166(a) (1-5) and 211.166 (b).

Transdermal Patches

Two of the three batch sizes for each strength should be at least 10 percent of the proposed commercial production batch (with packaging) or 25,000 units (for each strength), whichever is greater. The third batch can be smaller than 10 percent of the proposed commercial batch (with packaging), but should not be less than 60 percent of the pilot scale batch (with packaging). For transdermal matrix products, where different strengths are identified by the transdermal patch size (surface area), to comply with the three batch size recommendation, we recommend providing data on patches manufactured using three distinct matrix laminates at the time of submission (each laminate can be cut to support multiple strengths in the application, where applicable). We recommend you contact the appropriate OGD review division if you are manufacturing transdermal patches using other technologies (e.g., reservoir).[14]

You should include a representative sample from all three batches using different components of backing, adhesives, release liner, and other critical excipients used in packaging a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

[12] Amount packaged = 50 L or 30 L –(minus) filling/flushing loss.
[13] Ibid.
[14] See the guidance for industry on *Residual Drug in Transdermal and Related Drug Delivery Systems*.

Topicals

(a) Creams/Lotions/Gels: For nonsterile semi-solid dosage forms,[15] the two pilot scale batches should be at least 100 Kg or 10 percent of the production batch, whichever is larger, packaged.[16] The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 40 percent of the pilot scale batch, packaged.[17] Packaging requirements are also discussed in 21 CFR 211.166(a) (1-5) and 211.166 (b).

(b) Inhalation Solutions/Nasal Sprays (nasal nonmetered dose atomizer): Please refer to the following guidances for industry for information: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, and *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.[18]

Please contact OGD to discuss other dosage forms and/or routes of administration not covered in this document.

Q14: Is it acceptable to use a technical grade of the drug substance for the small scale batches or one of the two pilot scale batches of finished drug product?

A14: No. The applicant should follow CGMP requirements for ANDA submission as they relate to drug substance and finished drug product. Because the drug substance quality can affect the drug product stability, the drug substance used for the ANDA batches (supporting the application) should be of the same quality intended for the market product. We would consider data from the use of a different grade drug substance for a product as supporting data.

Q15: Do the small scale batches need to be manufactured in accordance with all CGMP regulations, or is it acceptable to manufacture the small scale batches in a research setting?

A15: All ANDA submission batches should be made following CGMP.

Q16: Should the small scale batches meet the same finished product specification as the pilot scale batches?

A16: Yes. The finished product specification should be the same for all three ANDA submission batches submitted.

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[15] See the CDER Data Standards Manual, Drug Nomenclature Monographs (Dosage Form) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm.

[16] Amount packaged = 100 Kg or Larger –(minus) filling/flushing loss.

[17] Ibid.

[18] See footnote 2.

Q17: For sterile products, is it acceptable to manufacture the small scale batches in a nonsterile facility and allow variance from sterility and particulate criteria?

A17: No. To be consistent with ICH Q1A(R2), sterile product small scale batches should be representative of the manufacturing processes to be applied to a full production scale batch, and therefore should not be manufactured in a nonsterile facility. Sterility is a critical quality attribute (CQA) for sterile products.

Q18: Should small scale batches be produced at the proposed commercial site?

A18: Yes. Small scale batches should be produced at the proposed commercial site. The primary batch information submitted in the application is used to support the proposed commercial product manufacture. Product batches produced at a different site than the proposed commercial site would not be considered as primary batches.

Q19(i): In cases where an intermediate bulk material is identical between the various strengths (dose proportional blends, bulk solutions, etc.), is it sufficient to perform stability on one lot of each strength, when each strength is produced from a separate intermediate bulk?

A19(i): No. For ANDAs that contain multiple strengths (that are dose proportional), three separate intermediate bulk granulations (or blends) should be manufactured. One batch of bulk granulation (or blend) should be used to manufacture all the strengths proposed. The other two bulk granulations (or blends) can be used to manufacture only the lowest and the highest strengths, in addition to the strength used in BE studies (i.e., the strength(s) tested in the BE studies should have three batches). Stability testing should still use all three batches of drug product.

Q19(ii): Are differences in the capsule shell (i.e., imprint, color, size, etc.), allowed in cases where a multi-strength capsule product is dose-proportional across all strengths (based on common bead blend)?

A19(ii): Yes differences in the capsule shell are allowed in the described case.

Q20: What are the criteria for an exception to the recommendations regarding minimum size for pilot scale for ANDA submission batches? What justification would be needed if we wanted to deviate from these guidance recommendations?

A20: The submission ANDA batches can have a smaller size than the established pilot scale, according to the ICH definition, when any one of the following circumstances prevails:

- The reference listed drug product has an orphan drug designation.

- Use of a controlled drug substance is based on a Drug Enforcement Administration allocation.
- The test batch size is the same as the commercial batch size with the commitment that a prior approval supplement (PAS) will be provided when there is a scale-up.

Q21: Are scale-up and postapproval changes (SUPAC) level one and two variations and changes permitted among the three ANDA submission batches for components and composition?

A21: No. The three ANDA submission batches should maintain the chosen formula based on product development studies for components and composition.

Q22: Can FDA provide specific examples of cases where statistical analysis is required and the type of statistical analysis needed?

A22: The FDA stability guidance recommends analysis of data in accordance with ICH Q1E, Appendix A. The flowchart in that guidance provides clear situations where analysis is normally recommended or unnecessary. In addition, ICH Q1E B.7 figures provide example diagrams for assay and degradation products that illustrate how plots should be generated for the three batches using regression lines and upper and lower confidence limits.

Q23: How many batches of drug product should be tested for split-portions of scored tablets?

A23: In general, one batch testing for each scored strength on the split tablets will suffice, as recommended in the guidance for industry, *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[19]

Q24: For drug products that include placebo tablets, how many batches (of placebo tablets) are required for submission? Is 6 months of stability data on the placebo tablets needed if the ANDA is submitted after the June 2014 deadline?

A24: One batch of placebo tablets with full CMC information should be included at the time of ANDA submission; however, the final packaging presentation (containing the placebo tablets) should have data from accelerated and long-term stability testing. Six months of accelerated and long-term stability data are recommended for the entire packaging presentation including placebo tablets, where applicable, at the time of submission.

D. Amendments to Pending ANDA Application

Q1: What are the recommendations for amendments and responses filed to pending ANDAs after issuance of the final FDA stability guidance?

[19] See footnote 2.

A1: All amendments submitted to pending ANDAs after the effective date of the final FDA stability guidance will be held to the standards in place concerning stability data at the time of the original ANDA submission, unless there is a concern with the submitted stability data.

E. Stability Studies

Q1: What will be the expected testing time points on accelerated conditions?

A1: The applicant should test at 0 (initial release), 3, and 6 months; for additional time points on accelerated conditions, please follow ICH Q1A(R2) recommendations for all ANDAs.[20]

Q2: Can the Agency clarify expectations for the storage positions for products placed into the stability program?

A2: For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position. For routine stability studies, the applicant should pick the worst case orientation for the study.

Q3: When and how are reconstitution/dilution studies performed?

A3: Recommendations listed in ICH Q1A(R2), section II, B, 7, Storage Conditions (2.2.7) should be followed for all three batches. These studies should be performed when the drug product is labeled for reconstitution or dilution.

Q4: What types of containers are classified as semipermeable containers, and can the Agency clarify the stability expectations for the drug products in semipermeable containers?

A4: Examples of semipermeable containers are provided in the ICH Q1A(R2) glossary. The recommendations for stability expectations for semipermeable containers are detailed in ICH Q1A(R2) section II, B, 7, c. Drug products packaged in semipermeable containers (2.2.7.3).

Q5: Can the Agency clarify expectations around the number of batches to support tests such as preservative effectiveness and extractable leachable testing?

A5: One of the primary batches of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the end of the proposed shelf life. The drug product specification should

[20] This recommendation also applies to nasal spray, inhalation solution, suspension, aerosols, and liposomal drug products.

include a test for preservative content, and this attribute should be tested in all stability studies.

Extraction/leachable studies are generally one-time studies; however, if multiple types of containers/closures are employed for packaging, then additional studies could be recommended.

Q6: When are in-use stability studies needed?

A6: Please refer to response A3 under section E, Stability Studies.

Q7: Are there changes to postapproval protocols and commitments when ICH stability guidances are implemented because of scale or type of batches submitted?

A7: ICH Q1A(R2), section II, B, 8, Stability Commitment (2.2.8) addresses this question. Section 2.1.8 provides information regarding stability commitment for drug substances.

Also, ANDAs and DMFs should include a commitment to place one batch of drug product and drug substance, respectively, into the annual long-term stability program, and to provide stability data in the annual reports.