
Guidance for Industry

Changes to an Approved NDA or ANDA

Questions and Answers

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

**January 2001
CMC**

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This guidance represents the Food and Drug Administration'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.

This document provides questions and answers relating to the guidance on *Changes to an Approved NDA or ANDA* (the guidance).² The questions are based on those posed to CDER by applicants. The questions and answers are presented using subject headings that correspond to the table of contents in the guidance.

REPORTING CATEGORIES

Q1: *For a change that is reported in a Supplement — Changes Being Effected in 30 Days, will CDER complete the review of the supplement within 30 Days?*

A1: Within 30 days CDER will notify the applicant that prior approval is required for the change (i.e., CDER has designated the supplement a prior approval supplement) or that the FDA has determined appropriate information is missing, including information that should have been developed by the applicant in assessing the effects of the change. Supplement reviews will be performed consistent with standard procedures. It is unlikely that a substantive review and action letter will be completed within 30 days.

¹ This guidance has been prepared by the Chemistry, Manufacturing, and Controls committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

² A notice of availability for this guidance published in the *Federal Register* on November 23, 1999 (64 FR 65716). The guidance provides information on how to report changes that are made to an approved new drug application (NDA) or abbreviated new drug application (ANDA). Questions on the *Changes to an Approved NDA or ANDA* guidance can be submitted by e-mail to pac314_70@cder.fda.gov.

Q2: *If information is missing from a Supplement — Changes Being Effected in 30 Days, will the reporting category be changed to a prior approval supplement?*

A2: No. If FDA informs the applicant within 30 days of receipt of the *Supplement — Changes Being Effected in 30 Days* that information is missing, the reporting category is not changed to a prior approval supplement. However, distribution of the product made with the change must be delayed until the supplement is amended with the missing information.

Q3: *A change (specified change) is planned. The guidance recommends that the change be reported in a supplemental application. However, the data generated indicate that this change does not adversely affect the identity, strength, quality, purity, and potency of the product. Can this change be reported in an annual report?*

A3: No. The recommended reporting category is based on the *potential* for the change to adversely affect the identity, strength, quality, purity, or potency of the drug product as these factors relate to the safety or effectiveness of the drug product (see section 506A of the Federal Food, Drug, and Cosmetic Act (the Act)). CDER expects that the majority of the data and information submitted to support a supplemental change will, in the applicant's judgment, demonstrate that the change does not adversely affect the product. However, FDA will evaluate the completeness of the data and information and decide whether the applicant's conclusion (i.e., there is no adverse effect) is appropriate prior to approving such a change.

GENERAL REQUIREMENTS

Q1: *A manufacturing change is planned that can be reported in the annual report. Should the data to support the change be included in the annual report?*

A2: Yes. After the change is implemented, the information should be included in the next annual report. Moreover, the information to support the change must be generated prior to distributing the product made with the change (506A(b)). As stated in section 506A(b) of the Act, "a drug made with a manufacturing change (whether a major manufacturing change or otherwise) may be distributed only if, before distribution of the drug as so made, the holder involved validated the effects of the change on the identity, strength, quality, purity, and potency of the drug as the identity, strength, quality, purity, and potency may relate to the safety or effectiveness of the drug."

MANUFACTURING SITES

Q1: *Can a change in the manufacturing site for a drug substance that involves a different company (i.e., change in source) be reported in a Supplement — Changes Being Effected in 30 Days?*

A1: As stated in section VI.A of the guidance, “A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.” Typically, a change from one drug substance manufacturer to another involves more than simply a site change. In most cases, there will be additional differences (e.g., route of synthesis, process, solvents, equipment). Without extensive knowledge of the new and old sources (e.g., access to the drug master file), an applicant cannot adequately describe the differences between the sources or evaluate the multiple change. Therefore, when the applicant does not have extensive knowledge to provide the information and evaluation, the drug substance site change should be reported in a prior approval supplement. When an applicant has the extensive knowledge to describe the differences between the sources, the applicant can report the change as appropriate after evaluation as a multiple change. If the change is not reported in a prior approval supplement, the applicant should include a statement in the submission that the change involves no changes that should be reported in a prior approval supplement. In either case, a move to a drug substance manufacturing site should be reported in a prior approval supplement when the site does not have a satisfactory current good manufacturing practice (CGMP) inspection (see guidance for details) for the type of operation.

Q2: *Should a change to a different site be reported when the change is for fabrication of packaging components?*

A2: Section VI.A of the guidance identifies the site changes that should be reported to CDER. A move to a different site to manufacture or process drug products should be reported. The guidance defines sites used to manufacture or process drug products to include sites used by the applicant (applicant owned or contractors) to **prepare** (e.g., sterilize, depyrogenate, irradiate, wash) container closure systems or packaging components. A change to a different site for fabricating packaging components (e.g., bottles) or manufacturing packaging materials (e.g., resins) need not be reported if there is no other change (e.g., dimensions, composition, specification, processing aids). If other changes occur, the reporting category should be based on the recommended reporting categories for the changes (i.e., the manufacturing site change should not be considered when determining the appropriate reporting category).

Q3: *The guidance states that a move to a different site that results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years should be reported in a prior approval supplement (section VI.B.1). Two manufacturing sites were approved in the original application. Production at one of the sites has not occurred in 5 years but is going to be restarted. Should this restart be reported in a prior approval supplement?*

A3: A restart of manufacturing at a site already approved in the application need not be reported in the application as long as the restart does not involve any other changes

(e.g., equipment, process) that should be reported. If the restart involves a site that is not approved in the application, a prior approval supplement should be submitted.

Q4: *A packaging site will be added that will enclose two sample cartons, along with some promotional material, into a larger carton or box preprinted with the product name:*

- *Does the information about the tertiary packaging site need to be submitted to the agency? If yes, can CDER be notified in an annual report?*
- *Is the tertiary site held to the same CGMP requirements as a secondary site? For example, if a tertiary site should be submitted to the agency, and this site has not had any CGMP inspection within the last two years, is this change still annual reportable?*

A4: The guidance only distinguishes between primary and secondary packaging sites. The site described would be considered a secondary packaging site. CGMP requirements extend beyond packaging and repackaging operations that involve direct product contact. For example, a site must register with FDA (21 CFR Part 207) and is subject to CGMP inspection (21 CFR Part 211) when the site is used to attach inserts, or in the case of a cartoning site, when cartons contain product labels. If registration and/or inspection are required for the site of this secondary packaging operation, CDER should be notified of the different site (via the application). The site should have a satisfactory inspection relating to packaging operations for notification to occur in the annual report. For the purposes of this guidance, in general, there is no two-year limit on the CGMP inspection (see Manufacturing Sites Q10). If registration and inspection are not required for the site of this secondary packaging operation, the applicant need not notify CDER of the site. If you have any questions on whether this packaging operation is subject to FDA registration or inspection, you should contact the appropriate CDER inspection and/or compliance staff for advice.

Q5: *Certain changes relating to contract sterilization sites for packaging components can be reported in an annual report (section VI.D.4). Does this also apply to applicant owned sites?*

A5: Yes. Whether the sterilization site is applicant- or contractor-owned, a change to a different sterilization site for packaging components can be reported in an annual report when the process is not materially different from the process described in the approved application, and the facility has a satisfactory CGMP inspection for the type of operation that is being performed.

Q6: *Should a prior approval supplement be submitted for a change in the sterilization site for a primary packaging component of a metered dose inhaler?*

A6: The change can be reported in an annual report as long as the process is not materially different from that provided for in the approved application and as long as the facility

has a satisfactory CGMP inspection for the type of operation being performed (section VI.D.4)

Q7: *If an intermediate or starting material is also a drug substance, would the recommendations on reporting site changes for intermediates or drug substances apply?*

A7: If a drug substance is used as an intermediate in a drug substance manufacturing process, the guidance on intermediates would apply. This assumes that the material has been classified appropriately as an intermediate (see relevant definitions in the glossary of the guidance). CDER traditionally does not consider a drug substance to be a starting material.

Q8: *Do the recommendations for manufacturing site changes apply to manufacturing sites outside the United States as long as the site has a satisfactory CGMP inspection for the type of operation that will be moved?*

A8: Yes. The recommendations in the guidance apply to domestic and foreign manufacturing sites.

Q9: *The site where the certificates of analysis and regulatory documentation are reviewed prior to commercial distribution of the product will be relocated. Should this site change be reported in the application?*

A9: A change in the site where GMP support paperwork operations occur need not be reported in the application.

Q10: *The guidance (section VI.B.2) states that a manufacturing site change should be submitted in a prior approval supplement if the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved. In previous guidances it was stated that a satisfactory CGMP inspection within the last two years was needed. Should a prior approval supplement be used if the new facility has a satisfactory CGMP inspection for the type of operation being moved, but the inspection occurred more than two years ago?*

A10: For the purposes of the guidance, there is no time limit on the satisfactory CGMP inspection unless the type of operation was discontinued (section VI.B.1).

Q11: *What is the reporting category for a change to a different manufacturing site for an excipient?*

A11: CDER need not be notified of this type of change.

Q12: *What is the recommended reporting category for the addition of a new aseptic filling line for sterile products?*

A12: The addition of a new aseptic filling line should be reported in a prior approval supplement (section VI.B.4).

Q13: *Why does the guidance exclude drug substance intermediates when referring to satisfactory CGMP inspections?*

A13: Section 510(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with CGMPs. No distinction is made between the manufacture of drug substance and drug product. Although the CGMP regulations under 21 CFR Parts 210 and 211 apply only to drug products, FDA expects appropriate CGMPs to be applied to all steps of a drug substance manufacturing process beginning with the use of starting materials. The types of sites identified in the guidance are routinely subject to FDA inspection with the exception of those facilities or establishments used to manufacture or process drug substance intermediates. Drug substance intermediate manufacturing or processing sites are not exempt from inspection, but an inspection is generally discretionary. Moreover, this type of facility is always subject to *for cause* inspection. Because drug substance intermediate sites are not routinely inspected, a satisfactory CGMP inspection was not included as a condition for submitting the change in a Supplement — Changes Being Effected in 30 Days or annual report. However, when a drug substance intermediate manufacturing or processing site has been inspected and the CGMP inspection was not satisfactory, the change in site should be submitted as a prior approval supplement.

MANUFACTURING PROCESS

Q1: *An applicant intends to add a coarse screen to the opening of a blender, through which all individual components of a granulation would pass prior to granulation. The applicant asks whether this could be considered a change in a control which would be reportable in a Supplement — Changes Being Effected under section VII.C.2.a of the guidance.*

A1: This change is not considered a change in control but an additional step in the manufacturing process. However, it is not considered a fundamental change in the manufacturing process. This type of change should be reported in a *Supplement — Changes Being Effected in 30 Days* (section VII.C.1.a).

Q2: *Can changes in mixing steps and elimination of a mixing step be reported in an annual report if these changes are implemented prior to the manufacture of validation batches?*

A2: The timing of the postapproval change (i.e., pre- or post validation batches) does not affect the recommended reporting category. The type of change should be submitted in either a *Supplement — Changes Being Effected in 30 Days* (e.g., VIII.C.1.a.) or

prior approval supplement (e.g., VII.B.1) depending on the specifics of each situation such as the type of dosage form.

Q3: *What is the recommended reporting category for a drug product (immediate release solid oral dosage form) scale change beyond 10 times the size of the biobatch? If the change is annual reportable, should the information identified in SUPAC-IR³ for a Level 1 scale change be submitted?*

A3: All changes in the scale of the nonprotein drug product manufacturing batches can be reported in an annual report (see section VII.D.1.a).⁴ However, if the scale change results in other changes (e.g., equipment, process), the change would be considered a multiple change, and the recommended reporting category should be the most restrictive of those for any of the individual changes (section XII). Recommendations on scale changes for protein drug products are included in section VII.C.1.c and VII.D.1.a of the guidance.

The information and data recommendations in SUPAC-IR can be used to support a change. However, the data and information that should be included in the annual report to support the change depends on the extent of the scale change. If the scale change is up to and including 10 times the size of the biobatch, the data and information recommended in SUPAC-IR section V.A (Level 1) should be submitted. If the scale up is greater than 10 times the size of the biobatch, the data and information recommended in SUPAC-IR Section V.B (Level 2) should be submitted.

Q4: *Can changes in the drying process (i.e., tray dryer to cone dryer and associated process changes) of the crude drug substance be reported in an annual report?*

A4: Section VII.B.5 of the guidance recommends a prior approval supplement when any change is made after the final intermediate processing step in the drug substance manufacture. Changes that occur after the final intermediate for synthetic or semisynthetic drug substances will be addressed in the guidance on Bulk Active Chemicals – Postapproval Changes II (BACPAC II). Until the BACPAC II guidance is finalized, the appropriate chemistry review division(s) can be consulted for advice if an applicant believes a change made after the final intermediate processing step is not a major change.

Q5: *For nonprotein drug substances, how should scale changes be reported when there are no other changes?*

³ Guidance on *Immediate Release Solid Oral Dosage Forms — Scale-Up and Post-Approval Changes; Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995).

⁴ The reporting categories in the *Changes to an Approved NDA or ANDA* guidance supersede those recommended in SUPAC guidances where there are inconsistencies. Therefore, the recommendations in SUPAC-IR that certain scale changes be submitted in supplements are superseded.

A5: Changes in the manufacturing scale for a nonprotein drug substance prior to the final intermediate need not be reported to CDER unless the change adversely affects the identity, strength, quality, purity, or potency of the drug product as these factors relate to the safety and effectiveness of the drug product. Changes in scale for synthetic or semisynthetic drug substances after the final intermediate will be addressed in the BACPAC II guidance. Until the BACPAC II guidance is finalized, the appropriate chemistry review division(s) can be consulted for advice if an applicant believes a change made after the final intermediate processing step is not a major change.

Q6: *Section VII.B.2 of the guidance recommends a prior approval supplement for changes in sterilizer and load configurations that are outside the range of previously validated loads. How should changes in load configuration for manufacturing process equipment (e.g., forceps, stopper bowl) be reported?*

A6: A Supplement — Changes Being Effected in 30 Days is recommended if the load change is large enough so that the cycle has to be adjusted beyond the previously validated range. If the cycle does not have to be adjusted, an annual report is recommended.

Q7: *Can CDER be notified in an annual report when the filling speed line for a sterile product is increased by changing the speed of filling through the fill heads or adding filling heads.*

A7: Changing the speed of filling through the fill heads or adding fill heads can be reported in an annual report as long as the total processing time is not extended beyond the validated limits in the approved application.

Q8: *A prior approval supplement is recommended for changes in the source material of drug substances or drug products derived from plants, animals, or microorganisms (section VII.B.3). Does this recommendation apply to a substance derived from a natural source that is used as the starting material for the synthetic part of a semi-synthetic process?*

A8: Yes. This recommendation applies to the starting materials for the synthetic part of a semi-synthetic process as well as a drug substance or drug product derived directly from these sources with no further synthetic modification. For example, the recommendation applies to changes in the source material for: (1) a plant extract that undergoes synthetic modification to produce the drug substance, or (2) a cellular metabolite that undergoes synthetic modification to produce an antibiotic drug substance. This recommendation does not apply to starting materials derived from natural sources that are widely available (i.e., used more than just to produce pharmaceuticals), such as glucose or tartaric acid, that can be used in a synthetic process.

SPECIFICATIONS

Q1: *How should a revision of an analytical procedure be reported to allow for the use of a company (i.e., secondary) standard in addition to the U. S. Pharmacopeia (USP) standard?*

A1: The revision of an analytical procedure to allow the option to use a secondary standard should be reported in an annual report. Also, the laboratory reference standards used must comply with CGMP regulations (e.g., 21 CFR 211.194(c)).

Q2: *How should a decrease in the fill volume be reported?*

A2: A change in the fill volume of a drug product involves a change to the specification and must be submitted in a prior approval supplement unless exempted by regulation or guidance (506A(c)(2)(A) of the Act). There is no exemption for this type of specification change; therefore, a prior approval supplement should be submitted.

Q3: *What reporting category should be used if a USP HPLC assay procedure replaces, or is used in addition to, a microbiological assay that is listed in the approved specification as the regulatory analytical procedure?*

A3: The addition of the HPLC analytical procedure to comply with an official compendium can be submitted in an annual report (section VIII.D.1). However, if the microbiological assay will also be deleted, the deletion of a test should be reported in a prior approval supplement (section VIII.B.2 and 3).

Q4: *In the approved application, it is specified that full product testing will be performed before bulk material is sent to a contract packager and when the packaged material is received from the contractor. Can notification in an annual report be used to replace the full testing of the product after it is received from the contractor with an identity test?*

A4: This change involves a deletion of tests and should be reported in a prior approval supplement (section VIII.B.2).

PACKAGE

Q1: *The plastic used in a desiccant canister is being changed. When the desiccant is used for bottles of solid oral dosage form products, should it be reported as a Supplement — Changes Being Effected under section IX.C.2.b of the guidance?*

A1: Section IX.C.2 b. states that a change in or addition to or deletion of a desiccant should be reported in a *Supplement — Changes Being Effected*. A change in desiccant refers to the type of desiccant used (e.g., silica gel, calcium chloride) or

amount. Changes in the plastic canister of a desiccant used in a solid oral dosage form product should be reported as recommended for changes in the plastic for the container closure system. Under certain circumstances these changes can be reported in an annual report (e.g., section IX.D.3).

Q2: *How should deletion of cotton filler from the bottles of a solid oral dosage form product be reported?*

A2: The deletion of a cotton filler is considered similar to the deletion of a desiccant and should be reported in a *Supplement — Changes Being Effected*.

Q3: *The guidance recommends notification in an annual report for a change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium. Does “protocol” refer to a comparability protocol or the approved stability protocol?*

A3: With respect to the guidance, the term protocol refers to tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of adverse effect on the identity, strength, quality, purity, and potency of the drug from specific types of changes. This type of protocol is often referred to as an equivalency protocol or comparability protocol. The approved stability protocol may be one part of the comparability/equivalency protocol to help demonstrate the absence of an adverse effect.

Q4: *Can a change from tri-layer to a bi-layer blister package for a solid oral dosage form be reported in an annual report when:*

- *The product contact surface will remain the same.*
- *The available data shows that the new package provides the same protective properties as the currently approved container closure system.*
- *The new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form products.*

A4: Based on the information provided, the change can be reported in an annual report (section IX.D.5). The annual report should include the necessary documentation that confirms the statements that the product contact surface remains the same and that the bi-layer blister package has the same or better protective properties as the tri-layer blister (e.g., light or moisture transmission, stability data).

Q5: *The guidance recommends notification in an annual report when there is a change to a new container closure system, and the container closure system is already approved in the NDA or ANDA for other strengths of the product (section IX.D.3). Is the word product intended to mean the same formulation of the product, and can the products be approved in different NDAs or ANDAs?*

- A5: The word *product* as used in this example is intended to mean products that have the same basic formulation. These formulations may be proportionally different due to a difference in strength. When different strengths of the same product are approved in different applications from the same applicant, the changes can still be reported in an annual report.

MISCELLANEOUS CHANGES

Q1: The guidance recommends an annual report for the addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period. If these changes are made in an annual report, is the protocol still considered approved?

- A1: Yes. If changes such as these are made in an annual report, the stability protocol is still considered approved.

Q2: How should the addition of a test to an approved stability protocol be reported?

- A2: When a test is added, whether it is added to a release specification or a stability protocol, the change should be reported in a *Supplement — Changes Being Effected* under section VIII.C.2.a of the guidance, which states "An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion."