
Guidance for Industry

CMC Postapproval

Manufacturing Changes To Be Documented in Annual Reports

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

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CMC

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Guidance for Industry CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports

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**U.S. Department of Health and Human Services
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Guidance for Industry¹ CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports

This guidance represents 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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes to be documented in annual reports. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely have a minimal potential to have an adverse effect on product quality² and, therefore, should be documented by applicants in an annual report.^{3,4}

Appendix A lists examples of CMC postapproval manufacturing changes previously submitted under manufacturing supplements that we have determined generally to be of low risk to product quality. Appendix B provides examples of minor changes to be documented in an annual report that were previously published in FDA's Scale-up and Postapproval Changes (SUPAC) guidances and other postapproval change CMC guidances (see Section V. Resources for a list of those guidances).

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.

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

² In this guidance, the term "product quality" refers to drug product identity, strength, quality, purity, or potency, as these factors may relate to the safety or effectiveness of the drug product.

³ See 21 CFR 314.70(d).

⁴ This guidance excludes positron emission tomography (PET) drug products. See the guidance for industry, [PET Drugs — Current Good Manufacturing Practice \(CGMP\)](#), for information about PET drug products. CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

An applicant must notify FDA of a change to an approved application in accordance with all statutory and regulatory requirements—including section 506A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356a) (FD&C Act), which was added by section 116 of the Food and Drug Administration Modernization Act,⁵ and 21 CFR 314.70. Section 506A of the FD&C Act provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. Under 21 CFR 314.70, all postapproval CMC changes beyond the variations provided for in an approved NDA and ANDA are categorized into one of three reporting categories: major, moderate, or minor.

If a change is considered to be major, an applicant must submit and receive FDA approval of a supplemental application to the NDA or ANDA before the product made with the manufacturing change is distributed (also known as a prior approval supplement (PAS)). If a change is considered to be moderate, an applicant must submit a supplement at least 30 days before the product is distributed (CBE-30 supplement) or, in some cases, submit a supplement at the time of distribution (CBE-0 supplement).⁶ If a change is considered to be minor, an applicant may proceed with the change, but must notify FDA of the change in an annual report. For any change, applicants must assess the effects of the change on product quality through appropriate studies. For additional background information regarding the reporting categories for NDAs and ANDAs, see FDA's guidance for industry on [*Changes to an Approved NDA or ANDA*](#) (April 2004).

In our September 2004 final report, [*Pharmaceutical Current Good Manufacturing Practices \(CGMPs\) for the 21st Century – A Risk-Based Approach*](#) (Pharmaceutical Product Quality Initiative), the Agency stated that to keep pace with the many advances in quality management practices in manufacturing and to enable the Agency to more effectively allocate our limited regulatory resources, we would implement a cooperative, risk-based approach for regulating pharmaceutical manufacturing. As part of this approach, the Agency determined that to provide the most effective public health protection, our CMC regulatory review should be based on an understanding of product risk and how best to manage this risk.

In addition to the requirements in section 506A of the FD&C Act and 21 CFR 314.70, applicants are required to comply with other applicable laws and regulations, including the Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMP) regulations in 21 CFR Parts 210 and 211.

III. DISCUSSION

The number of CMC manufacturing supplements for NDAs and ANDAs has continued to increase over the last several years. In connection with FDA's Pharmaceutical Product Quality Initiative and our risk-based approach to CMC review, we have evaluated the types of changes that have been submitted in CMC postapproval manufacturing supplements and determined

⁵ Public Law 105-115.

⁶ CBE is changes being effected.

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that many of the changes being reported present low risk to the quality of the product and do not need to be submitted in supplements.

Based on our risk-based evaluation, we developed a list (see Appendix A) to provide additional current recommendations to companies regarding some postapproval manufacturing changes for NDAs and ANDAs that may be considered to have a minimal potential to have an adverse effect on product quality, and, therefore, may be classified as a change to be documented in the next annual report (i.e., notification of a change after implementation) rather than in a supplement.

The changes listed in Appendix A are categorized according to the type of manufacturing change. These changes are either additions or revisions to the CMC changes recommended for documentation in an annual report that were previously published in the guidance for industry on *Changes to an Approved NDA or ANDA*, the SUPAC guidances, and other related guidances (see Section V. Resources). Thus, before you submit a supplement based on recommendations provided in these previously published guidances, you also should refer to the list of risk-based recommendations that are provided in Appendix A of this guidance. These recommendations clarify whether submission of a supplement or documentation of the change in an annual report may be appropriate.

We expect NDA and ANDA holders to evaluate the specific change that they are planning to make in the context of their particular circumstances to determine whether the proposed change would present a minimal potential to have an adverse effect on product quality. When a risk-based evaluation shows that the proposed change would have a minimal potential to have an adverse effect on product quality, the change can be documented in the next annual report. An NDA or ANDA holder may, based on their specific circumstances, decide that a change described in Appendices A and B would more appropriately be submitted as a supplement rather than in an annual report. In such cases, changes should be reported to the Agency according to the results of the risk-based evaluation and 21 CFR 314.70. Accordingly, we consider this guidance to provide recommendations for changes that are appropriately documented in an annual report rather than to establish a requirement to document these changes in annual reports pursuant to 21 CFR 314.70(a)(3).⁷

To the extent that a recommendation in this guidance to document a single change in an annual report is found to be inconsistent with previously published FDA guidances, the reporting category recommended in this guidance would apply, assuming that the applicant's proposed change would present a minimal potential to have an adverse effect on product quality. For changes not addressed in this guidance, or for multiple related changes implemented simultaneously, applicants should refer to other CDER guidances (see Section V. Resources), as well as Appendix B, to determine the appropriate reporting categories (i.e., PAS, CBE-30, CBE-0, or annual report) for notifying the Agency of the changes.

⁷ Under 21 CFR 314.70(a)(3), an applicant is required to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change. In this guidance, we are asking applicants to use scientific data from appropriate studies and risk analysis to determine whether changes should be submitted in a PAS, CBE-30, CBE-0, or annual report.

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Applicants should note FDA's recommendations for active pharmaceutical ingredient manufacturing that are provided in the guidance for industry, [*O7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*](#) (August 2001). CGMP regulations for finished pharmaceuticals contain specific requirements relevant to the types of changes addressed in this guidance, and compliance with the CGMP regulations is required regardless of how the change is reported to the Agency. CGMP requirements include establishing and following appropriate written procedures reviewed and approved by the quality unit, qualifying equipment as suitable for its intended use, using validated test methods, scientifically establishing the commercial manufacturing process, and ensuring the manufacturing process's ongoing state of control (which may include additional process validation and stability studies depending on the nature of the change).⁸

If you have specific questions associated with whether or not the change should be submitted to the Agency in a supplement or documented in an annual report, we recommend that you contact the appropriate CDER review division in the Office of New Drug Quality Assessment, the Office of Generic Drugs, or OPS's New Drug Microbiology Staff.

IV. CONTENTS OF ANNUAL REPORT NOTIFICATION

To document changes in an annual report in accordance with 21 CFR 314.81(b)(2)(iv)(b) and 314.70(d)(3), the applicant must include a full description of the CMC changes that were made that the applicant believes did not require a supplemental application under sections 314.70(b) and (c). This description should include:

- A list of each change and the date each change was implemented; and
- Relevant summary of data from studies and tests performed to assess the effects of each change on product quality, including (where applicable) a list of cross-references to change control and change validation protocols and standard operating procedures (SOPs) that were used to assess or demonstrate the effect of the change.

The description also should include:

- The name(s) of one or more drug products affected or involved in the change (e.g., different label strengths/product presentations); or
- Reference to any previously approved grouped supplements if the change affected multiple products.

Executed batch records, SOPs, and data from studies and tests performed to assess the effects of each change should be kept on file and made available to the Agency on request (e.g., during an inspection). The applicant should describe each change in an annual report in enough detail to allow the Agency to efficiently determine whether the appropriate reporting category has

⁸ See 21 CFR 210 and 211.

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been used. If the submitted change is inappropriate for documentation in an annual report, the applicant will be notified of the correct category and additional information may be requested.

V. RESOURCES

Provided below are other FDA guidances that discuss reporting of CMC postapproval changes. They should be referred to in addition to this guidance.

- FDA guidances applicable to the CMC section of a drug application:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>

In prior CMC postapproval changes guidance documents, recommendations are provided for changes in components and composition, manufacturing sites, manufacturing process, specifications, container/closure system, labeling, miscellaneous changes, and multiple related changes.

- **PAC-ATLS: Postapproval Changes – Analytical Testing Laboratory Sites**, dated April 28, 1998,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070582.pdf>.
- **SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation**, dated November 1995,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070636.pdf>.
- **SUPAC-IR Questions and Answers about SUPAC-IR Guidance**, dated February 18, 1997,
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm>.
- **SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum**, dated January 1999,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070637.pdf>.
- **SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation**, dated September 1997,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070640.pdf>.

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- **SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation**, dated May 1997, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf>.
- **SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum**, dated December 1998, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070928.pdf>.
- **Changes to an Approved NDA or ANDA: Questions and Answers**, dated January 2001, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM122871.pdf>.
- **Changes to an Approved NDA or ANDA, Revision 1**, dated April 2004, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf>.
- **Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes**, dated November 2004, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070544.pdf>.

VI. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The expiration of the OMB control number will be updated periodically.

The total number of supplements submitted per year is estimated to reduce based on the recommendations in the guidance because certain changes submitted as supplements would now be documented in annual reports. Therefore, for such changes, the information collection with respect to the submission of supplements will be reduced. Because the number of supplements per year is estimated to reduce, the total number of hours for preparing supplements would correspondingly reduce. Send comments regarding this burden estimate or suggestions for reducing this burden to:

The Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4178, Silver Spring, MD 20993-0002.

This guidance also refers to previously approved collections of information found in FDA regulations: (1) The submission of supplements to FDA for certain changes to an approved application in accordance with 21 CFR 314.70 and 314.71; (2) the submission of annual reports

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to FDA (Form FDA 2252) in accordance with § 314.81(b)(2); (3) the submission of supplements to an approved ANDA for changes that require FDA approval; and (4) other post-marketing reports for ANDAs in accordance with § 314.98(c), of which the estimate for annual reports is included under § 314.81(b)(2). FDA currently has OMB approval for these collections of information under OMB Control Number 0910-0001.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0001. The current expiration date is available at <https://www.reginfo.gov> (search ICR and enter OMB control number).

APPENDIX A: EXAMPLES OF CMC POSTAPPROVAL MANUFACTURING CHANGES TO BE DOCUMENTED IN ANNUAL REPORTS IF THEY HAVE A MINIMAL POTENTIAL TO HAVE AN ADVERSE EFFECT ON PRODUCT QUALITY

1. Components and Composition

- 1.1. Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses.
- 1.2. Change in coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved for another similar product⁹ and the change does not alter release of the drug, specification (i.e., tests, analytical procedures, and acceptance criteria for test results), or stability.
- 1.3. In instances where the supplier of an inactive ingredient was specified in an approved application, change to a new supplier of that inactive ingredient (e.g., change from one drug master file (DMF) holder to other DMF holder or change to a new qualified supplier). This is applicable only if the inactive ingredient's specification remains unchanged.

2. Manufacturing Sites

- 2.1. Minor structural modifications made in the sterile product manufacturing facility approved in an application that do not affect a product manufacturing area or sterility assurance and do not change product quality or specification.
- 2.2. In the manufacturing of sterile products, the addition of barriers within a conventional fill area to prevent routine in-process human intervention in an existing filling or compounding area that is qualified and validated by established procedures.

3. Manufacturing Process, Batch Size, and Equipment

- 3.1. The following process changes:
 - 3.1.1. Addition of a sieving step(s) for aggregates removal if it occurs under nonaseptic conditions.
 - 3.1.2. Changes in mixing times (for blending powders, granules) for immediate-release solid oral dosage forms and solution products.¹⁰
 - 3.1.3. Changes in drying times for immediate-release solid oral dosage forms.

⁹ See the *Inactive Ingredient Database*, available on FDA's web site at www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

¹⁰ Note the requirement for finished pharmaceuticals to establish and follow procedures regarding adequacy of mixing to assure uniformity and homogeneity for appropriate dosage forms per 21 CFR 211.110(a).

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- 3.2. Manufacturing batch size or scale change that results from combining previously separated batches (or lots) of in-process material to perform the next step in the manufacturing process if all combined batches meet the approved in-process control limits, the next step remains unaffected, and appropriate traceability is maintained.
 - 3.3. For equipment used in aseptic manufacturing processes (e.g., new filling line, new lyophilizer), replacement of equipment with that of the same design and operating principle, when there is no change in the approved process methodology or in-process control limits.
 - 3.4. Addition of identical processing lines that operate parallel to each other in the drug substance and drug product manufacturing process with no change in in-process control limits or product specification.
 - 3.5. For sterile drug products, addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of filter integrity test failures.
 - 3.6. Decrease in the number of open handling steps or manual operation procedures, when it reduces risk to product and there is no other change to the process (e.g., implementation of aseptic connection devices to replace flame protection procedures).
 - 3.7. For sterile drug products, changes to the ranges of filtration process parameters (such as flow rate, pressure, time, or volume, but not pore size) that are within currently validated parameters ranges and therefore would not warrant new validation studies for the new ranges.
 - 3.8. In the manufacture of sterile drug products, change from a qualified sterilization chamber (ethylene oxide (EtO), autoclave) to another of the same design and operating principle for the preparation of container/closure systems, sterilization of “change parts” for processing equipment, and terminal sterilization of product, when the new chamber and load configurations are validated to operate within the previously validated parameters. This does not include situations that change the validation parameters.
4. Specifications
- 4.1. Addition of a new test to the specification for an excipient
 - 4.2. Change to the specification for a drug substance, drug product, or pharmacopeial excipient that is made to comply with the official compendia if it is a change that does not relax an acceptance criterion or delete a test.

Specification changes not suitable for documentation in an annual report include changes to an assay, tests for impurities, degradation products, product-related substances, or biological activities that are approved in NDAs and ANDAs. Such changes should be submitted in a supplement.

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- 4.3. Change in the approved analytical procedure if the revised method maintains the original test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims to have or is represented to possess and the acceptance criteria remain unchanged (e.g., change in the flow rate or sample preparation for a high performance liquid chromatography (HPLC) method).
- 4.4. Replacement of a nonspecific identity test with a discriminating identity test that includes a change in acceptance criteria (e.g., replacing *SDS-PAGE*¹¹ with peptide map).
- 4.5. Addition of an in-process test.
- 4.6. Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that ensures adequacy of mix.
- 4.7. Revision of tablet hardness (e.g., acceptance criterion for test result or change to a different analytical procedure and its associated acceptance criterion for test result) if there is no change in the approved dissolution analytical procedure, criteria, or associated dissolution profile.
- 4.8. Addition of a test for packaging material to provide increased assurance of quality.
- 4.9. Tightening of an approved acceptance criterion for a drug substance, a drug product, drug product formulation components, and in-process material.
5. Container/Closure System
 - 5.1. A change in the container/closure system for the storage of a nonsterile drug substance (solid, semisolid, or liquid) when the proposed container/closure system has no increased risk of leachable substances in the extractable profile (for semisolids and liquids) and equivalent protection properties for the packaged material.
 - 5.2. Use of or transfer to a contract manufacturing organization (CMO) for the washing, drying, or/and siliconization of a drug product stopper or any part of a container closure system, provided the applicant certifies that the CMO's processes have been validated and the CMO's site has been audited and found CGMP compliant by the applicant (or by another party sponsored by the applicant)..
 - 5.3. For solid oral dosage forms, when the change is to use another suitable primary packaging component used in any other CDER-approved drug product:
 - 5.3.1. Change in type of desiccant to another desiccant that was previously used in another approved product and is suitable for its intended use.

¹¹ *SDS-PAGE* stands for sodium dodecyl sulfate polyacrylamide gel electrophoresis.

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- 5.3.2. Elimination of a bottle filler, such as a fibrous material (e.g., suitable type of cotton, rayon, polyester, etc.) that is used to fill empty or void space in the finished product container.
- 5.4. For parenteral drug products, a change in glass supplier without a change in glass type or coating and without a change in container/closure dimensions.
- 5.5. Changes to a crimp cap (ferrule and flip cap/overseal), provided that there are no changes to the color and that the container and closure integrity have been demonstrated using a validated test method. Note, however, that a change in the flip cap/overseal color to make it consistent with an established color coding system for that class of drug products is to be documented in an annual report.
- 5.6. Change to delete the company trademark or other markings on the crimp cap (ferrule and flip cap/overseal) to comply with the official compendium.
- 6. Labeling Changes
 - 6.1. Revision in drug product labeling to reflect the qualitative change in inactive ingredient(s) of coating formulation, as recommended in 1.2 above. The final Structured Product Labeling (SPL) reflecting the qualitative change should be submitted to the Agency when implementing this change to allow for maintenance of the current product information in eLIST.¹² This will help ensure the safe and effective use of the drug product.
 - 6.2. A change in the drug product labeling to revise information related to CMC changes discussed in this guidance. If the change involves associated revision of drug product labeling, 6.1 above would apply.
- 7. Miscellaneous Changes
 - 7.1. Extension of the drug substance retest dating period or drug product expiration dating period based on real-time stability data from pilot-scale or larger/commercial-scale batches following an approved stability protocol.
 - 7.2. For immediate release solid oral dosage forms, if a dissolution test is performed, elimination of a test for identity or hardness from an approved stability protocol.
 - 7.3. For changes in an application that are fully consistent in scope and requirements with changes previously approved in a grouped supplement (also defined as a Bundled Supplement), the same applicant can make the same change to similar drug products.¹³

¹² See www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM164094.pdf.

¹³ See MAPP 5015.6, "Review of the Same Supplemental Change to More Than One NDA or ANDA in More Than One Review Division," January 2000, www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm079567.pdf.

APPENDIX B: EXAMPLES OF CHANGES TO BE DOCUMENTED IN AN ANNUAL REPORT FROM FDA’S SUPAC-IR, SUPAC-MR, SUPAC-SS, AND CHANGES TO AN APPROVED NDA OR ANDA GUIDANCES

1. Components and Composition

- 1.1. Any change made to comply with the official compendium, except relaxation of an acceptance criterion or deletion of a test (see 21 CFR 314.70(c)(2)(iii)).
- 1.2. Complete or partial deletion of an ingredient intended to affect only the color, flavor, or fragrance of the drug product without change in other approved specification. Note that a deletion or change in color, flavor, or fragrance also may affect the appearance and other noticeable organoleptic properties (visual appearance, taste, flavor, odor, or fragrance) of the dosage form. These changes may affect the “How the Drug Product is Supplied” section of labeling. In such cases, reporting of revision or change as described in Appendix A, 6. Labeling Changes, also would apply.
- 1.3. Change in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation approved in the original application, less than or equal to the following percent ranges: Filler $\pm 5\%$, Disintegrant (Starch $\pm 3\%$, Other $\pm 1\%$), Binder $\pm 0.5\%$, Lubricant (Calcium or Magnesium Stearate $\pm 0.25\%$, Other $\pm 1\%$), Glidant (Talc $\pm 1\%$, Other $\pm 0.1\%$), and Film Coat $\pm 1\%$.
- 1.4. Change in the supplier of an excipient, where the technical grade and specification for the excipient remain the same.
- 1.5. Changes in release controlling excipients less than or equal to 5% expressed as a percentage (w/w) of total release controlling excipients approved in the original application of a modified-release solid oral dosage form. After the change, the total weight of the dosage form and its specification would remain the same as originally approved.

2. Manufacturing Site

- 2.1. When the new site has a satisfactory CGMP inspection status for the type of operation¹⁴ involved, the following changes can be documented in an annual report:
 - 2.1.1. A move to a different manufacturing site for secondary packaging, labeling, ink imprinting on a solid oral dosage form, and manufacture or processing of drug substance intermediates other than the final intermediate.
 - 2.1.2. Change in location of manufacturing (including terminal sterilization of finished product) within the same facility or site for both company-owned and contract manufacturers that do not include any scale-up changes, changes in manufacturing process or equipment, or changes in components and

¹⁴ See the guidance to industry, *Changes to an Approved NDA or ANDA*, Appendix B.

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composition of drug product. The standard operating procedures, personnel with suitable experience with the manufacturing processes, environmental conditions and controls, and manufacturing batch records will remain the same except for administrative information and the location within the same facility or site.

3. Manufacturing Process

- 3.1. For drug products, change to equipment of the same design and operating principles, capacity, and/or batch size (increase or decrease), except for natural protein drug substances and natural protein drug products.
- 3.2. Change in the order of addition of drug product components for solution dosage forms (except active pharmaceutical ingredients) or change in the order of ingredients added to solutions used in unit operations (e.g., granulation solutions).

4. Specifications

- 4.1. For drug substance and drug product, the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application or deletion of an alternative analytical procedure.
- 4.2. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.