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# **Guidance for Industry**

## **Changes to an Approved NDA or ANDA**

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

**April 2004**

**CMC**

**Revision 1**

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# Guidance for Industry

## Changes to an Approved NDA or ANDA

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<http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services  
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## **Guidance for Industry<sup>1</sup>**

### **Changes to an Approved NDA or ANDA**

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 it 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.

\*\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect. If you have any questions about the effect of any portion of this guidance, contact the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (HFD-003), Food and Drug Association, 5600 Fishers Lane, Rockville, MD 20857.

#### **I. INTRODUCTION AND BACKGROUND**

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for postapproval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) labeling, as well as (7) miscellaneous changes and (8) multiple related changes.

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry

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<sup>1</sup> This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

**Paperwork Reduction Act Public Burden Statement:** 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 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0538 (until August 31, 2005).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

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entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).<sup>2</sup>

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).<sup>3</sup> Section 116 of the Modernization Act amended the the Act by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The FDA has revised its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act.

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a drug product as these factors may relate to the safety or effectiveness of the drug product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.<sup>4</sup>

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on ***reporting categories*** in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act and § 314.70(c) provide for two types of changes-being-effected supplements (see section II), while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes-being-effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended reporting categories or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

FDA's guidance documents, in general, 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. Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect. If you

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<sup>2</sup> FDA is currently revising the 1997 guidance and intends to issue it in draft for public comment.

<sup>3</sup> Public Law 105-115.

<sup>4</sup> A list of CDER guidances is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

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have any questions about the effect of any portion of this guidance, contact the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (HFD-003), Food and Drug Association, 5600 Fishers Lane, Rockville, MD 20857.

## **II. REPORTING CATEGORIES**

Section 506A of the Act and § 314.70 provide for four reporting categories that are distinguished in the following paragraphs.

A **major change** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a **Prior Approval Supplement** (§ 314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a **Prior Approval Supplement - Expedited Review Requested** (§ 314.70(b)(4)).<sup>5</sup> FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A **moderate change** is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a **Supplement - Changes Being Effected in 30 Days** (§ 314.70(c)(3)). The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (§ 314.70(c)(5)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (§ 314.70(a)(2) and (c)(4)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended to provide the missing information (§ 314.70(c)(5)(ii)).

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (§ 314.70(c)(6)). This type of supplement is called, and should be clearly labeled, a **Supplement - Changes Being Effected**. If, after review, FDA disapproves a changes-being-effected-in-30-days supplement or changes-being-effected supplement, FDA may order the

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<sup>5</sup> Internal Agency policies and procedures relating to processing requests for expedited review of supplements to approved ANDAs and NDAs are documented in CDER's Manual of Policies and Procedures (MAPP) at 5240.1 and 5310.3, respectively. MAPPs can be located on the Internet at <http://www.fda.gov/cder/mapp.htm>.

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manufacturer to cease distribution of the drug products made using the disapproved change (§ 314.70(c)(7)).

A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next ***Annual Report*** (§ 314.70(d)).

Under § 314.70(e), an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, studies, and acceptance criteria to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol that was not approved as part of the original application must be submitted as a prior approval supplement (314.70(e)). On February 25, 2003, FDA issued a draft guidance on comparability protocols entitled *Comparability protocols - Chemistry, Manufacturing, and Controls Information*.

### **III. GENERAL REQUIREMENTS**

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (§ 314.70(a)(1)).

A supplement or annual report must include a list of all changes contained in the supplement or annual report. On the list, FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter (§ 314.70(a)(6)). In annual reports, the list should be included in the summary section (§ 314.81(b)(2)(i)). The applicant must describe each change fully in the supplement or annual report (§ 314.70(a)(1)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the *Code of Federal Regulations* (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

A changes-being-effected supplement providing for labeling changes under § 314.70(c)(6)(iii) must include 12 copies of the final printed labeling (§ 314.70(c)(1)). In accordance with

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§ 314.70(a)(4), an applicant also must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with § 314.70(b) or (c).

Except for supplements providing only for a change in labeling, an applicant must include in each supplement and amendment to a supplement a statement certifying that a field copy has been provided in accordance with 21 CFR 314.440(a)(4)<sup>6</sup> (§ 314.70(a)(5)).

### **IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES**

#### **A. Assessment of the Effects of the Change**

The holder of an approved application under section 505 of the Act *must assess the effects of the change before distributing a drug product made with a manufacturing change* (§ 314.70(a)(2)).<sup>7</sup> For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (section 506A(b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act). The type of information that must be included in a supplemental application or an annual report is specified in § 314.70(b)(3), (c)(4), and (d)(3).

##### *1. Conformance to Specifications*

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.<sup>8</sup> A *specification* is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. *Acceptance criteria* are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the

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<sup>6</sup> Mailing information for field copies is provided in 21 CFR 314.440(a)(4). FDA recommends that the *applicant's home FDA district office* referred to in the regulations be the district office where the applicant's headquarters is located.

<sup>7</sup> *Assess the effects of the change* means to evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors relate to the safety or effectiveness of the drug product. The terms *assess* or *assessment* as used in this guidance are not the same as validation. Certain validation information, such as for sterilization processes, is considered information that is needed to assess the effect of the change as specified in § 314.70(a)(2) and should be submitted in an NDA or ANDA. Unless otherwise specified by FDA, validation (e.g., process, equipment) data need not be submitted in the application, but should be retained at the facility and be available for review by FDA at the Agency's discretion under CGMPs.

<sup>8</sup> If a specification needs to be revised as a result of the change, this would be considered a multiple change (see sections VIII and XII).

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material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

#### **2. *Additional Testing***

In addition to confirming that the material affected by manufacturing changes continues to meet its specification, we recommend that the applicant perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the material directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the drug product. For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.<sup>9</sup>
- Evaluation of the hardness or friability of a tablet after certain changes.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

#### **B. *Equivalence***

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, and potency of the

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<sup>9</sup> Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances (e.g., ICH Q3B *Impurities in New Drug Products* (November 1996)).

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drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the drug product made after the change equivalent to the drug product made before the change?

An exception to this general approach is that when bioequivalence is redocumented for certain ANDA postapproval changes, FDA recommends that the comparator be the reference listed drug. Equivalence comparisons frequently have a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, *equivalent* does not necessarily mean *identical*. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

#### **C. Adverse Effect**

Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, FDA recommends that ***the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change***. For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification.<sup>10</sup> The applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. Even so, we recommend that the applicant submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the drug product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the drug product.

#### **V. COMPONENTS AND COMPOSITION**

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance (§ 314.70(b)(2)(i)). The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report (§ 314.70(d)(2)(ii)). Guidance on changes in components and composition that may be submitted in a changes-being-effected supplement or annual report is not included in this document because

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<sup>10</sup> Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances.

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of the complexity of the recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

### **VI. MANUFACTURING SITES<sup>11</sup>**

#### **A. General Considerations**

CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). Sites can include those used by an applicant to (1) manufacture or process drug products,<sup>12</sup> in-process materials, drug substances, or drug substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. FDA recommends that the supplement or annual report identify whether the proposed manufacturing site is an alternative to or replacement for the site or sites provided for in the approved application.

FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a *satisfactory CGMP inspection*<sup>13</sup> for the *type of operation*<sup>14</sup> being moved (see sections VI.B.1 and 2).

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations,

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<sup>11</sup> See Attachment A for a discussion of the definition of *same manufacturing site* and *different manufacturing site*.

<sup>12</sup> Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components. Changes in the site used to fabricate packaging components (e.g., bottles) or manufacture packaging materials (e.g., resins) need not be reported to CDER if there are no other changes (e.g., dimensions, compositions, processing aids). If other changes occur, the reporting category should be based on the recommended reporting categories for these changes (i.e., the manufacturing site change does not need to be considered when determining the appropriate reporting category).

<sup>13</sup> See Glossary for a definition of *satisfactory CGMP inspection*.

<sup>14</sup> See Attachment B for a discussion of the term *type of operation*.

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the potential for adverse effect depends on factors such as the type of drug substance or drug product and operation being performed. Therefore, recommended reporting categories may differ depending on the type of drug product and operations.

Except for the situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, construction activities at a manufacturing site or moving production operations within a building or between buildings at the same manufacturing site do not have to be reported to CDER.

We recommend that a move to a manufacturing site that involves other changes (e.g., process, equipment) be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

#### **B. Major Changes (Prior Approval Supplement)**

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.
2. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,<sup>15</sup> transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.
4. Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved drug products. An example

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<sup>15</sup> Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form drug products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

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would be transferring the manufacture of a lyophilized drug product to an existing aseptic process area where no approved lyophilized drug products are manufactured or where the approved lyophilized drug products being manufactured have different container types and/or sizes than the container of the drug product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

5. Transfer of the manufacture of a finished drug product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar drug product types and processes may be submitted as a changes-being-effected-in-30-days supplement (see section VI.C.1.a).

### **C. Moderate Changes (Supplement - Changes Being Effected)**

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2), then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement.

1. *Supplement - Changes Being Effected in 30 Days*
  - a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.
  - b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site except as provided for in section VI.B.4.
  - c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products.
  - d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation

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samples), and (3) the new testing facility has the capability to perform the intended testing.

#### **2. *Supplement - Changes Being Effected***

A move to a different manufacturing site for the manufacture or processing of the final intermediate.

#### **D. Minor Changes (Annual Report)**

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved, then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement (see sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging.
2. A move to a different manufacturing site for labeling.
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate.
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.

## **VII. MANUFACTURING PROCESS**

### **A. General Considerations**

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there may be a substantial potential for adverse effect regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change must be submitted in a prior approval supplement (section 506A(c) of the Act).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

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### **B. Major Changes (Prior Approval Supplement)**

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.
2. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:
  - Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
  - Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
  - Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
  - Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
  - Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be submitted as a changes-being-effected-in-30-days supplement.
  - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.
  - Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
  - Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.
  - Changes in sterilizer load configurations that are outside the range of previously validated loads.

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.



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- Changes in materials or pore size rating of filters used in aseptic processing.
3. The following changes for a natural product:<sup>16</sup>
- Changes in the virus or adventitious agent removal or inactivation methods. This applies to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
  - For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
  - For drug substance and drug product, establishment of a new master cell bank or seed.
4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:
- a. Drug product
    - Dry to wet granulation or vice versa.
    - Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).
  - b. Drug substance
    - Filtration to centrifugation or vice versa.
    - Change in the route of synthesis of a drug substance.
5. The following changes for drug substance
- Any process change made after the final intermediate processing step in drug substance manufacture.
  - Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.
6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on ***CDER-approved drug products***.<sup>17</sup>

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<sup>16</sup> For the purposes of this guidance, *natural product* refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms, and that are subject to approval under section 505 of the Act. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

<sup>17</sup> See Attachment C for a discussion of *CDER-approved drug products*.

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

### *Contains Nonbinding Recommendations\**

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

#### **C. Moderate Changes (Supplement - Changes Being Effected)**

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. *Supplement - Changes Being Effected in 30 Days*
  - a. For drug products, any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.
  - b. For drug substances, any change in process and/or process parameters except as otherwise provided for in this guidance.
  - c. For natural protein drug substances and natural protein drug products:
    - Any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance (e.g., section VII.B.5, VII.D.7).
    - An increase or decrease in production scale during finishing steps that involves different equipment.
    - Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters.
  - d. For sterile drug products, drug substances, and components, as appropriate:
    - Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products that are produced by terminal sterilization processes or aseptic processing.
    - Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) when additional validation studies for the new parameters should be performed.
    - Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk.

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### ***Contains Nonbinding Recommendations\****

- Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that result in changes to validated operating parameters (time, temperature,  $F_0$ , and others).
  - Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.
- e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

#### **2. *Supplement - Changes Being Effected***

- a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.
- b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.

### **D. Minor Changes (Annual Report)**

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. For drug products, changes to equipment of the same design and operating principle and/or changes in scale except as otherwise provided for in this guidance (e.g., section VII.C.1.c, VII.D.7).
2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.
3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products.
4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form.
5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

### ***Contains Nonbinding Recommendations\****

6. Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.
7. For natural protein drug products and natural protein drug substances:
  - An increase or decrease in production scale during finishing steps that does not involve an equipment change.
  - Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.

## **VIII. SPECIFICATIONS**

### **A. General Considerations**

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (§ 314.70(b)(2)(i)). *Specifications* (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of defining specifications, *acceptance criteria* are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and an acceptance criterion are, respectively, an assay, a specific, fully described high pressure liquid chromatography (HPLC) procedure, and a range of 98.0–102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.<sup>18</sup>

A *regulatory* analytical procedure is the procedure in the approved application that is designated for use in evaluating a defined characteristic of the drug substance or drug product. Section 501(b) of the Act recognizes the analytical procedures in the *U.S. Pharmacopeia/National Formulary* (USP/NF) as the regulatory analytical procedures for compendial items. Tests and associated acceptance criteria and regulatory analytical procedures in addition to those specified in the USP/NF may be required for approving compendial items (section 505 of the Act).

The applicant may include in its application *alternatives* to the approved regulatory analytical procedures for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, regulatory analytical procedures are used.

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<sup>18</sup> See FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

## *Contains Nonbinding Recommendations\**

In sections B through D below, the use of the term *analytical procedure* without a qualifier such as *regulatory* or *alternative* refers to an analytical procedure used to test materials other than the drug substance or drug product.

### **B. Major Changes (Prior Approval Supplement)**

The following are examples of changes in specifications considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Relaxing an acceptance criterion except as otherwise provided for in this guidance (e.g., section VIII.C.1.b, VIII.C.1.e).
2. Deleting any part of a specification except as otherwise provided for in this guidance (e.g., section VIII.D.2).
3. Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.
4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.
5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide 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 except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) an HPLC procedure that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) an HPLC procedure that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.
6. Relating to testing of raw materials for viruses or adventitious agents:<sup>19</sup> (1) relaxing an acceptance criterion, (2) deleting a test, or (3) a change in the analytical procedure that does not provide 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.

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<sup>19</sup> In this context, testing for adventitious agents is not considered to include tests that are found in an official compendium (e.g., USP <61>).

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

## *Contains Nonbinding Recommendations\**

### **C. Moderate Changes (Supplement - Changes Being Effected)**

The following are examples of changes in specifications considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

#### *1. Supplement - Changes Being Effected in 30 Days*

- a. Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.
- b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) except as provided for in section VIII.B.6.
- c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide 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 except as provided for in section VIII.B.6.
- d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.
- e. Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (§ 314.70(c)(2)(iii)).

#### *2. Supplement - Changes Being Effected*

- a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

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### ***Contains Nonbinding Recommendations\****

- b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the 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.

#### **D. Minor Changes (Annual Report)**

The following are examples of changes in specifications considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. Any change in a specification made to comply with an official compendium, except the changes described in section VIII.C.1.e, that is consistent with FDA statutory and regulatory requirements (§ 314.70(d)(2)(i)).
2. 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.
3. Tightening of acceptance criteria.
4. 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.

## **IX. CONTAINER CLOSURE SYSTEM**

### **A. General Considerations**

The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification.

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

### ***Contains Nonbinding Recommendations\****

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

#### **B. Major Changes (Prior Approval Supplement)**

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for an ophthalmic ointment.
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form and same route of administration **and** with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).
3. A change in the primary packaging components for any drug product when the primary packaging components control<sup>20</sup> the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).
4. For sterile drug products, any change that may affect drug product sterility assurance, such as:<sup>21</sup>
  - A change from a glass ampule to a glass vial with an elastomeric closure.

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<sup>20</sup>A container closure system that is considered to control the dose delivered to the patient is a container closure system where the system itself, rather than a person, regulates the amount of drug product ultimately delivered to a patient. A container closure system where a person controls the amount of drug product administered or that allows verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) is not considered a container closure system that controls the dose delivered to the patient.

<sup>21</sup> Some of these identified changes, depending on the circumstances, may have to be submitted as original NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.



### ***Contains Nonbinding Recommendations\****

- A change to a flexible container system (bag) from another container system.
  - A change to a prefilled syringe dosage form from another container system.
  - A change from a single unit dose container to a multiple dose container system.
  - Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
  - Changes in the size and/or shape of a container for a sterile drug product.
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases) or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product.
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

### **C. Moderate Changes (Supplement - Changes Being Effected)**

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

#### *1. Supplement - Changes Being Effected in 30 Days*

- a. A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product.
- b. Changes in the size or shape of a container for a sterile drug substance.
- c. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in a unit-of-use container.<sup>22</sup>

#### *2. Supplement - Changes Being Effected*

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<sup>22</sup>A unit-of-use container is one that contains a specific quantity of a drug product and is intended to be dispensed to the patient without further modification except for the addition of appropriate labeling.

\* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect.

### ***Contains Nonbinding Recommendations\****

- a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2), without a change from one container closure system to another (§ 314.70(c)(6)(ii)).
- b. A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container,<sup>23</sup> except for solid dosage forms (see section IX.D.3) .
- c. A change in or addition or deletion of a desiccant.

#### **D. Minor Changes (Annual Report)**

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. 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 (§ 314.70(d)(2)(v)).
2. A change in the size and/or shape of a container for a nonsterile solid dosage form (§ 314.70(d)(2)(iv)).
3. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container.
4. The following changes in the container closure system of solid oral dosage form drug products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products:<sup>24</sup>
  - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.

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<sup>23</sup>A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion. This type of container is not distributed directly to patients but is used by health care practitioners who dispense the drug product in smaller amounts to a patient in accordance with a physician's instructions.

<sup>24</sup> For sections IX.D.4 to IX.D.7, changes in the container closure system that result in drug product contact with a component material that has never been used in any CDER-approved drug product of the same type should be submitted as a changes-being-effected-in-30-days supplement (section IX.C.1) or prior approval supplement (section IX.B.1).

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- Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).
  - Changes in packaging materials used to control odor (e.g., charcoal packets).
  - Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).
  - Increasing the wall thickness of the container.
  - A change in or addition of a cap liner.
  - A change in or addition of a seal (e.g., heat induction seal).
  - A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form drug products.
  - A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product.
5. The following changes in the container closure system of nonsterile liquid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid drug products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical drug products):
- Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
  - Increasing the wall thickness of the container.
  - A change in or addition of a cap liner.
  - A change in or addition of a seal (e.g., heat induction seal).
6. A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved drug products of the same type (e.g., solid oral dosage form, rectal suppository).
7. The following changes in the container closure system of nonsterile semisolid drug products as long as the new package provides the same or

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better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid drug products:

- Changes in the closure or cap.
  - Increasing the wall thickness of the container.
  - A change in or addition of a cap liner.
  - A change in or addition of a seal.
  - A change in the crimp sealant.
8. A change in the flip seal cap color as long as the cap color is consistent with any established color coding system for that class of drug products.

## **X. LABELING**

### **A. General Considerations**

A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with § 314.70(a)(4), an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) or (c) of § 314.70. All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.

### **B. Major Changes (Prior Approval Supplement)**

Any proposed change in the labeling, except changes designated as moderate or minor by regulation or guidance, must be submitted as a prior approval supplement (§ 314.70(b)(2)(v)(A)). If applicable, any change to a Medication Guide required under 21 CFR part 208, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv), must be submitted in a prior approval supplement (§ 314.70(b)(v)(B)). The following list contains some examples of changes currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.

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5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another drug product.
7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

**C. Moderate Changes (Supplement - Changes Being Effected)**

Under § 314.70(c)(6)(iii), a changes-being-effected supplement must be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence,

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### ***Contains Nonbinding Recommendations\****

psychological effect, or overdose, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the drug product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) normally requires a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision. A changes-being-effected supplement that provides for a labeling change under §§ 314.70(c)(6)(iii) must include 12 copies of final printed labeling (§ 314.70(c)(1)). The following list includes some examples of changes currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.
2. Addition of a precaution arising out of a postmarketing study.
3. Clarification of the administration statement to ensure proper administration of the drug product.

#### **D. Minor Changes (Annual Report)**

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report (§ 314.70(d)(2)(ix) and (d)(2)(x)). The following list includes some examples currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling.
2. Editorial changes, such as adding a distributor's name.
3. Foreign language versions of the labeling if no change is made to the content of the approved labeling and a certified translation is included.
4. Labeling changes made to comply with an official compendium.

## **XI. MISCELLANEOUS CHANGES**

### **A. Major Changes (Prior Approval Supplement)**

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

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1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug (§ 314.70(b)(2)(ii)).
2. Addition of a stability protocol or comparability protocol.
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).
4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.
5. Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application (§ 314.70(b)(2)(viii)).

#### **B. Moderate Changes (Supplement - Changes Being Effected)**

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

##### *1. Supplement - Changes Being Effected in 30 Days*

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product.  
Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application.

##### *2. Supplement - Changes Being Effected*

No changes have been identified.

#### **C. Minor Changes (Annual Report)**

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

1. An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application (§ 314.70(d)(2)(vi)).

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### *Contains Nonbinding Recommendations\**

2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.
3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.
4. Non-USP reference standards:
  - Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
  - Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency.

## **XII. MULTIPLE RELATED CHANGES**

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

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*Contains Nonbinding Recommendations\**

**ATTACHMENT A: MANUFACTURING SITES**

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An *establishment* means a place of business under one management at one general physical location (§ 207.3(a)(7)). A *general physical location* is reasonably construed to include separate buildings within the same city *if* the activities in the buildings are closely related to the same business enterprise, are under the supervision of the same local management, and are all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms *same manufacturing site* and *different manufacturing site* mean:

**Domestic Establishments**

*Same manufacturing site:*

- The new and old buildings are included under the same drug establishment registration number<sup>25</sup>

*and*

- The same FDA district office is responsible for inspecting the operations in both the new and old buildings.

*Different manufacturing site:*

- The new and old buildings have different drug establishment registration numbers

*or*

- Different FDA district offices are responsible for inspecting operations in the new and old buildings.

For domestic establishments, the terms *same manufacturing site* and *different manufacturing site* supersede the terms *contiguous campus*, *same campus*, and *different campus* as used in the SUPAC guidances.

**Foreign Establishments**

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<sup>25</sup> The registration number is the number assigned to the establishment as part of the registration process (e.g., ORA Field Management Directive No. 92).

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***Contains Nonbinding Recommendations\****

Foreign establishments are not currently required to register with the FDA. On May 14, 1999, FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until registration of foreign establishments is required, same and different manufacturing sites mean:

*Same manufacturing site:*

- A contiguous or unbroken site or a set of buildings in adjacent city blocks.

*Different manufacturing site:*

- The new and old buildings are not on a contiguous site or not in adjacent city blocks.

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## *Contains Nonbinding Recommendations\**

### **ATTACHMENT B: TYPE OF OPERATION AND CGMP INSPECTIONS**

Section VI states that a change to a different manufacturing site should be submitted in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A *profile class system* is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below). However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term *type of operation* refers to the specialized or even unique conditions and practices that are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all drug products at a given manufacturing site. The conditions and practices, both general and specific, are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and drug products may be produced at a manufacturing site, or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a *profile class code*.

Generally, a satisfactory CGMP status for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in-process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site

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***Contains Nonbinding Recommendations\****

producing a terminally sterilized small volume parenteral drug product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if the rating for a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

|            |   |            |  |
|------------|---|------------|--|
| ADM        | Aerosol dispensed medication                                    | NEC        | Not elsewhere classified (when using this class, specific drug products are noted) |
| CBI        | Biotechnology crude drug  | OIN        | Ointment, nonsterile (includes cream, jelly, paste)                                |
| CEX        | Plant/animal extraction crude drug                              | POW        | Powders (includes oral and topical)  |
| CFS        | Sterile bulk by fermentation crude drug                         | RAD        | Radiopharmaceutical  |
| CFN        | Nonsterile bulk by fermentation crude drug                      | <b>RSP</b> | <b>Radiation sterilization process</b>   |
| CHG        | Capsule, prompt release   | SNI        | Sterile noninjectable  |
| CRU        | Crude bulk drugs-nonsynthesized                                 | SOP        | Soap   |
| CSG        | Capsules, soft gelatin  | <b>SSP</b> | <b>Steam sterilization process</b>   |
| CSN        | Nonsterile bulk by chemical synthesis                           | SUP        | Suppositories  |
| <b>CSP</b> | <b>Chemical sterilization process</b>                           | SVL        | Small volume parenterals (lyophilized)   |
| CSS        | Sterile bulk by chemical synthesis                              | SVS        | Sterile-filled small volume parenterals  |
| <b>CTL</b> | <b>Control testing laboratories</b>                             | SVT        | Terminally sterilized small volume parenteral                                      |
| CTR        | Capsules, modified-release                                      | TCM        | Tablets, prompt-release  |
| GAS        | Medical gas (includes liquid oxygen and other)                  | TCT        | Tablets, delayed-release   |
| <b>GSP</b> | <b>Gas sterilization process</b>                                | TDP        | Transdermal patches  |
| <b>HSP</b> | <b>Dry heat sterilization process</b>                           | <b>TSP</b> | <b>Fractional (tyndallization) sterilization process</b>                           |
| LIQ        | Liquid (includes solutions, suspension, elixirs, and tinctures) | TTR        | Tablets, extended-release  |
| LVP        | Large volume parenterals  | <b>WSP</b> | <b>Water sterilization process</b>   |

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)

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Examples of postapproval manufacturing site changes and recommended reporting categories:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be submitted in a prior approval supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out packaging operations for immediate-release tablets (TCM) and capsules (CHG) and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet drug products should be submitted in a prior approval supplement. The packaging site change for the capsule drug products should be submitted as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form drug products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the drug products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form drug products, is considered to apply to all dosage forms, including those not actually produced at the site. The consolidation can be submitted in a changes-being-effected-in-30-days supplement if the change is consistent with the recommendations in section VI.C.1.d.

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## **ATTACHMENT C: CDER-APPROVED DRUG PRODUCTS**

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved drug products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a drug product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. For example, certain changes in the container closure systems of solid oral dosage form drug products may be included in an annual report as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products (see section IX.D.4). If the new primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form drug products, then submission of the change in an annual report is not recommended.

CDER-approved drug products are considered those drug products subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, *Inactive Ingredient Guide*, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved drug product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, the applicant has the option of submitting the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, submitting similar changes for other NDAs and ANDAs using the lower recommended reporting category.

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## GLOSSARY

**Acceptance Criteria:** Numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3(b)).

**Active Ingredient/Drug Substance:** Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

**Assess the Effects of the Change:** To evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product (21 CFR 314.3(b)).

**Container Closure System:** The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product.

**Component:** Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

**Drug Product:** A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

**Final Intermediate:** The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance involves covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.

**Inactive Ingredient:** Any intended component of the drug product other than an active ingredient.

**In-process Material:** Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).

**Intermediate:** A material that is produced during steps of the synthesis of a drug substance and undergoes further molecular change before it becomes a drug substance.

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**Package:** The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).

**Packaging Component:** Any single part of a container closure system.

**Primary Packaging Component:** A packaging component that is or may be in direct contact with the dosage form.

**Reference Listed Drug:** The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3(b)).

**Satisfactory Current Good Manufacturing Practice (CGMP) Inspection:** A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found (No Action Indicated (NAI)) or (2) objectionable conditions were found, but voluntary corrective action is left to the firm and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP contains information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing (21 CFR 20.40(a)) and should be prepared following the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available on the Internet at <http://www.fda.gov/opacom/backgrounders/foiahand.html>.

**Secondary Packaging Component:** A packaging component that is not and will not be in direct contact with the dosage form.

**Specification:** The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product (21 CFR 314.3(b)).

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