Guidance for Industry

CMC Postapproval Manufacturing Changes Reportable in Annual Reports

DRAFT GUIDANCE

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

June 2010
CMC

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I. INTRODUCTION

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes that may be reported in annual reports. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely present minimal potential to have adverse effects on product quality and, therefore, may be reported by applicants in an annual report.[2,3]

Appendix A lists the CMC postapproval manufacturing changes previously submitted under manufacturing supplements that we have determined to be generally of low risk to product quality (product identity, strength, quality, purity, and potency as they relate to the safety or effectiveness of the product).

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

II. BACKGROUND

An applicant must notify FDA of a change to an approved application in accordance with all statutory and regulatory requirements—including section 506A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356a) (the Act), which was added by section 116 of the Food and

[1] This guidance has been prepared by the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] See 21 CFR 314.70(d).
[3] This guidance excludes positron emission tomography (PET) drug products. See the guidance for industry, *PET Drugs — Current Good Manufacturing Practice (CGMP)*.

Drug Modernization Act,[4] and 21 CFR 314.70. Section 506A of the Act provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. Under 21 CFR 314.70, all postapproval CMC changes beyond the established variations in an approved NDA and ANDA are categorized into one of three reporting categories: major, moderate, or minor.

If a change is considered to be major, an applicant must submit and receive FDA approval of a supplement before the product made with the manufacturing change is distributed. If a change is considered to be moderate, an applicant must submit a supplement at least 30 days before the product is distributed or, in some cases, submit a supplement at the time of distribution. If a change is considered to be minor, an applicant may proceed with the change, but must notify FDA of the change in an annual report. For any change, applicants must assess the effects of the change as they relate to product safety and efficacy and demonstrate those effects through appropriate studies to determine whether it would be more appropriate to submit a supplement. For additional background information regarding the reporting categories for NDAs and ANDAs, see FDA's guidance for industry on *Changes to an Approved NDA or ANDA* (April 2004).[5]

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

In addition to the requirements in section 506A of the Act and 21 CFR 314.70, applicants are required to comply with other applicable laws and regulations, including the CGMP for Finished Pharmaceutical regulations in 21 CFR Parts 210 and 211.

III. DISCUSSION

The number of CMC manufacturing supplements for NDAs and ANDAs has continued to increase over the last several years. In connection with FDA's Pharmaceutical Product Quality Initiative and our risk-based approach to CMC review, we have evaluated the types of changes that have been submitted in CMC postapproval manufacturing supplements and determined that many of the changes being reported present very low risk to the quality of the product and do not need to be submitted in supplements.

Based on this recent evaluation, we developed a list (see Appendix A) to provide current recommendations to companies regarding which postapproval manufacturing changes for

[4] Public Law 105-115.

[5] CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

NDAs and ANDAs may be considered to have a minimal potential for an adverse effect on the identity, strength, quality, purity, or potency of the drug product and, therefore, may be classified as a change reportable in an annual report (e.g., notification of a change after implementation) rather than in a supplement. The changes are categorized according to types of manufacturing changes and are either additions or revisions to the classification of changes listed in the guidance, *Changes to an Approved NDA or ANDA*.

Thus, if you are submitting supplemental applications that are based on the recommendations for CMC changes provided in *Changes to an Approved NDA or ANDA*, you also should refer to the list of risk-based recommendations that are provided in Appendix A of this guidance to determine if a particular change may now be reported in an annual report.[6] In addition, the recommendations in this guidance should help clarify when to submit a supplement and when a change may be reported in an annual report.

We expect NDA and ANDA holders to evaluate the specific change that they are planning to make in the context of their particular circumstances to determine whether the proposed change would present a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. Based on such an analysis, an NDA or ANDA holder may decide that a change described in Appendix A would more appropriately be submitted as a supplement rather than in an annual report. We, therefore, consider this guidance to provide recommendations for changes that may be appropriately submitted in an annual report rather than to provide a mandatory requirement for reporting these changes in annual reports pursuant to 21 CFR 314.70(a)(3).[7]

Applicants should remember that regardless of the reporting category for the postapproval manufacturing change, they are required to comply with the CGMP for Finished Pharmaceuticals regulations at 21 CFR Parts 210 and 211. Also, applicants should note FDA's recommendations for active pharmaceutical ingredient manufacturing that are provided in the guidance for industry, *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.* CGMP regulations for finished pharmaceuticals contain specific requirements relevant to the types of changes addressed in this guidance, and compliance with the CGMP regulations is required regardless of how the change is reported to the Agency. CGMP requirements include the need to qualify equipment as suitable for its intended use, the need to assure validated test methods and ongoing state of control of manufacturing processes, and the requirement to maintain appropriate written procedures that the quality unit has reviewed and approved.[8]

If you have specific questions associated with whether or not the change may be classified as requiring a supplement or is reportable in an annual report, we recommend that you contact the

[6] Note that the guidance, *Changes to an Approved NDA or ANDA*, will be revised to reflect these recommendations.

[7] Under 21 CFR 314.70(a)(3), an applicant is required to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change, but in this guidance we are asking sponsors to use judgment in determining which changes should be submitted in a prior approval supplement.

[8] See 21 CFR 210 and 211.

appropriate CDER review division in the Office of New Drug Quality Assessment (ONDQA), Office of Generic Drugs (OGD), or New Drug Microbiology Staff (OPS-NDMS).

IV. CONTENTS OF ANNUAL REPORT NOTIFICATION

To submit a notification of change in an annual report in accordance with 21 CFR 314.81(b)(2)(iv)(b) and 314.70(d)(3), the applicant must include a full description of the CMC changes that were made that the applicant believes did not require a supplemental application under sections 314.70(b) and (c). This description should include a (1) list of each change by the date the change was made; (2) relevant summary of data from studies and tests performed to evaluate the effects of the change, including cross references to validation protocols and standard operating procedures and policies; and (3) list of all drug products involved. The applicant should describe each change in an annual report in enough detail to allow us to quickly determine whether the appropriate reporting category has been used. In addition, the applicant should include the list of changes in the summary section of the annual report.[9] If the submitted change is inappropriate for an annual report, the applicant will be notified of the correct category and additional information may be requested.

[9] See 21 CFR 314.81(b)(2)(i).

APPENDIX A: CMC POSTAPROVAL MANUFACTURING CHANGES REPORTABLE IN ANNUAL REPORTS

1. Components and Composition

   1.1. Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses. Note that this does not apply to loss of potency during storage.

   1.2. Change in qualitative and quantitative coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved in another product[10] and the change in the formulation does not alter release of the drug.

   1.3. New supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged.

2. Manufacturing Sites

   2.1. Modification of an approved manufacturing facility that does not affect a product manufacturing area or sterility assurance and does not change product quality or specifications.

   2.2. Addition of barriers to prevent routine in-process human intervention in a filling or compounding area that is qualified and validated by established procedures.

   2.3. Manufacture of an additional drug product (including investigational or developmental products) in an approved multiple-product area that is producing another product(s) if:

      2.3.1. specific identity tests exist to differentiate between all products manufactured at the facility; and
      2.3.2. a change-over procedure between manufacturing processes is established; and
      2.3.3. the products do not represent an additional level of risk. Additional levels of risk might include, but are not limited to, the manufacture of highly toxic or potent products, highly immunogenic or allergenic products (e.g., penicillin), products that can accelerate degradation of another product (e.g., enzymes), products that represent a new or added risk for adventitious agents, or a product for adults added to a line manufacturing pediatric products.

3. Manufacturing Process

   3.1. Process changes including any of the following:

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

3.1.1. Addition of a sieving step(s) for aggregate removal if it occurs under nonaseptic conditions.

3.1.2. Changes in mixing times for immediate-release solid oral dosage forms and for solution products.

3.1.3. Changes in drying times for immediate-release solid oral dosage forms.

3.2. A scale change of pooled or separated batches to perform the next step in the manufacturing process if all batches meet the approved in-process control limits and the critical operating parameters for the next step remain unaffected.

3.3. Replacement of equipment with that of the same design and operating principle that does not affect the process methodology or in-process control limits, with the exception of equipment used in aseptic processing (e.g., new filling line, new lyophilizer).

3.4. Addition of a duplicate process chain or unit process in the drug substance and drug product manufacturing process with no change in in-process control limits or product specifications.

3.5. Addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of integrity test failures.

3.6. Reduction of open handling steps if there is an improvement with no change to the process (e.g., implementation of aseptic connection devices to replace flame protection procedures).

3.7. Changes to filtration process parameters (such as flow rate, pressure, time, or volume, but not filter materials or pore size) that are within currently validated parameters and therefore would not warrant new validation studies for the new parameters.

3.8. For sterile drug products, change from a qualified sterilization chamber (ethylene oxide (EtO), autoclave) to another of the same design and operating principle for container/closure preparation when the new chamber and load configurations are validated to operate within the previously validated parameters. This does not include situations that change the validation parameters.

4. Specifications

4.1. Addition of a specification for existing excipients.

4.2. Change to a drug substance or drug product to comply with the official compendia can be reported in an annual report if it is:

4.2.1. A change to tighten an existing acceptance criterion; or

4.2.2 Other changes, except for changes to assays, impurities, product-related substances, or biological activities in approved NDAs and ANDAs.

4.3. Change in the approved analytical procedure if the revised method maintains basic test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims to have or is represented to possess and the acceptance criteria remain unchanged (e.g., change in the flow rate or sample preparation for a high performance liquid chromatography (HPLC) method).

4.4. Replacement of a nonspecific identity test with a discriminating identity test that includes a change in acceptance criteria (e.g., replacing *SDS-PAGE*[11] with peptide map).

4.5. Addition of an in-process test.

4.6. Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that assures adequacy of mix.

4.7. Revision of tablet hardness if there is no significant change in the dissolution profile.

4.8. Elimination of an in-process disintegration test where a dissolution test is required for release.

4.9. Deletion of the homogeneity test as a routine test from the application, provided the applicant has process controls in place to demonstrate the product's homogeneity.

4.10. Addition of a test for packaging material to provide increased assurance of quality.

4.11. Tightening of an existing acceptance criterion.

5. Container/Closure System

5.1. A change in the container/closure system for the storage of a nonsterile drug substance when the proposed container/closure system has no increased risk of leachable substances in the extractable profile (for liquids) and equivalent protection properties.

5.2. Use of a contract manufacturing organization (CMO) for the washing of a drug product stopper, provided the applicant certifies that the CMO's washing process has been validated and the CMO's site has been audited by the applicant (or by another party sponsored by the applicant) and found CGMP compliant.

5.3. For solid oral dosage forms:

5.3.1. Elimination of bottle dunnage.

[11] *SDS-PAGE* stands for sodium dodecyl sulphate polyacrylamide gel electrophoresis.

5.3.2. Change in type of desiccant to another equivalent desiccant that was previously used in another approved product.

5.4. For parenteral drug products, a change in glass supplier without a change in glass type or coating and without a change in container/closure dimensions.

5.5. Changes to a crimp cap (ferrule and cap/overseal), provided that there are no changes to the labeling or the color and that container and closure integrity have been demonstrated using a validated test method.

6. Miscellaneous Changes

6.1. Extension of expiry based on real-time stability data from pilot scale batches following an approved stability protocol.

6.2. Reduction of expiration dating for a drug product for reasons other than stability failures.

6.3. If a dissolution test is performed, elimination of a nonstability indicating test for identity or hardness from an approved stability protocol.

6.4. For changes in an application that are fully consistent in scope and requirements with changes previously approved in a bundled supplement, the same applicant can add similar drug products. (See MAPP 5015.6, “Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division.”)