Postapproval Changes Related to Drug Product Quality, Manufacturing, and Controls that May Be Documented in Annual Reports

Rajendra (Raj) Uppoor, R.Ph., M.Pharm., Ph.D.
Office of Pharmaceutical Science
CDER, FDA

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Outline

- Background on the March 4, 2014 CMC guidance
- FDA's risk-based approach for regulating pharmaceutical manufacturing
- Annual report notification of the CMC changes made to the approved drug product
- **Postapproval manufacturing changes to be documented in annual reports if they have a minimal potential to have an adverse effect on product quality** - Examples

Background

- On June 25, 2010 (75 FR 36421) FDA announced the availability of the draft "Guidance for Industry, CMC Postapproval Manufacturing Changes Reportable in Annual Reports" and sought public comments
- Docket Number: **FDA-2010-D-0283**
- Approximately 340 comments were received
  (as itemized by CDER/OPS for review and analyses in order to finalize guidance)
- **Final "Guidance for Industry, CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports" was announced in 79 FR 12511, on March 5, 2014**
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217043.pdf

Guidance for Industry

CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports

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

March 2014
CMC

OMB Control Number 0910-0758
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(Expiration date will be updated periodically.)
See additional PRA statement in section VI of this guidance.

Guidance for Industry

CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

March 2014
CMC

Contains Nonbinding Recommendations

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Risk-Based Approach to the Regulation of Pharmaceutical Quality

- Stated in FDA"s "Pharmaceutical CGMPs for the 21st Century – **A Risk-Based Approach**" (September 2004 Report).
- **To keep pace with many advances in quality management practices in manufacturing** and **to enable the Agency to more effectively allocate its limited regulatory resources**, FDA would implement a **cooperative**, risk-based approach for regulating pharmaceutical manufacturing.
- To provide the most effective public health protection, **CMC regulatory review should be based on an understanding of product risk and how best to manage this risk**.

To Whom and What the Guidance Recommends

- Holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of CMC changes to be documented in annual reports.
- The guidance describes the postapproval manufacturing changes that **FDA has determined will likely have a minimal potential to have an adverse effect on product quality**, and therefore should be documented in an annual report.
- **For any postapproval CMC change, the applicants must assess the effects of the change** on product quality through appropriate studies before distributing the drug product made with the manufacturing change.

Assessment of Change is Required

- The holder of an approved application under section 505 of the Act must assess the effect of the change before distributing a drug product made with a manufacturing change [21 CFR 314.70(a)(2)].
- For each change, the supplement or annual report must contain information developed by the applicant that assesses the effects of the change. The FDA will determine whether this information is appropriate in support of the change.

Notification of Changes to NDAs and ANDAs is Required

- Notification to FDA is required for postapproval changes made to the CMC sections previously reviewed and approved, specifically, for changes beyond the variations provided for in an approved NDA or ANDA.
- FDA/CDER guidances have been published, including the SUPAC (scale-up and postapproval changes) guidances that provide recommendations on reporting categories (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm).
- Section 506A of the FD&C Act and 21 CFR 314.70 provide for **four reporting categories** to notify changes made in the CMC section(s).

Category of Change and Its Notification to FDA Using Form FDA 356h (Slide 1 of 3)

- **Major Change**: 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 its **approval by FDA prior to distribution of the drug product made using the change.** The supplement is called a **Prior Approval Supplement** [21 CFR 314.70(b)].

Category of Change and Its Notification to FDA using Form FDA 356h (Slide 2 of 3)

- **Moderate Change:** 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.
- **Two types:**
  - **Certain moderate changes requiring submission at least 30 days prior to distribution of the drug product made using the Change, Supplement – Changes Being Effected in 30 Days, CBE-30 Supplement [21CFR314.70(c)(3)].**
  - **Certain moderate changes for which distribution of drug product made with the change can occur when FDA receives the supplement, Supplement - Changes Being Effected, CBE-0 Supplement (21CFR314.70(c)(6)].**

If, after review, FDA disapproves a CBE-30 or CBE-0, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change [21CFR314.70(c)(7)].

Category of Change and Its Notification to FDA using Form FDA 356h or Form FDA 2252 (Slide 3 of 3)

- **Minor Change: 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**, **21 CFR §314.70(d)(3)** and **314.81(b)(2)(iv)(b).**

  (Form FDA 2252 is for Transmittal of Periodic Reports for Drugs for Human Use)
- Notwithstanding the requirements of paragraphs (b) and (c) of this section (§314.70), **an applicant must make a change provided for in those paragraphs in accordance with a regulation or a guidance that provides for a less burdensome notification of the change** (for example, by submission of a supplement that does not require approval prior to distribution of the product or in an annual report **[21 CFR 314.70(b)(3)]**.

Requirement to Comply with CGMP Regulations

- In addition to the requirements in Section 506A of the FD&C Act and 21 CFR 314.70, applicants are required to comply with other applicable laws and regulations, including the **Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMP)** regulations, stated in 21 CFR Parts 210 and 211.
- For example, **21 CFR 211.180(e), Records and Reports**: Written records required by this part shall be maintained so that **data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in the drug product specifications or manufacturing or control procedures**. Written procedures shall be established and follows for such evaluations and shall include provisions for (1) **A review of representative number of batches**, whether approved or rejected, and, where applicable, records associated with each batch. (2) A **review of complaints, recalls, returned or salvaged drug products, and investigations** conducted under §211.192 for each drug products.

CMC Topics Listed in FDA Postapproval Change Guidance

- Components and Composition
- Manufacturing Sites
- Manufacturing Process
- Specifications
- Container Closure System
- Labeling
- Miscellaneous Changes
- Multiple Related Changes

Contents of Annual Report Notification (Slide 1 of 2)

- The applicant must include a **full description of the CMC changes** that were made that the applicant believes did not require a supplemental application under sections 314.70(b) and (c). This description should include:
  - A **list of each change and the date each change was implemented**, and
  - Relevant **summary of data from studies and tests performed to assess the effects of each change** on product quality, including (where applicable) a list of cross-references to **change control** and **change validation protocols** and **SOPs** that were used to assess or demonstrate the effect of the change.
- The description should also include:
  - The **name(s) of one or more drug products affected or involved In the change** (e.g., different label strengths/product presentations), or
  - **Reference to any previously approved grouped supplements** if the change affected multiple products.

Contents of Annual Report Notification (Slide 1 of 2)

- **Executed batch records, SOPs and data from studies and tests performed** to assess the effects of each change **should be kept on file** and made available to the Agency on request (e.g., during an inspection).
- The applicant should **describe each change in an annual report in enough detail** to allow the Agency to efficiently determine whether the appropriate reporting category has been used. If the submitted change is inappropriate for documentation in an annual report, the applicant will be notified of the correct category and additional information may be requested by the Agency.

Examples of CMC Postapproval Manufacturing Changes to be Documented in Annual Reports

From Appendix A and Appendix B of the Guidance

Components and Composition

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

Manufacturing Sites

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

Manufacturing Process, Batch Size, and Equipment (Slide 1 of 2)

- **Process changes**
  - **Addition of sieving step(s) for aggregates removal**, under nonaseptic conditions
  - **Changes in mixing times** (for blending of powder, granules) **for IR solid oral dosage forms** and **solution products** (Note: Requirement for finished pharmaceuticals to establish and follow procedures regarding adequacy of mixing to assure uniformity and homogeneity for appropriate dosage forms per **21 CFR211.110(a)** continues to apply).
  - **Changes in drying times for immediate-release solid oral dosage forms**.
- Manufacturing batch size or scale change that results from **combining previously separated batches (or lots) of in-process material** to perform the next step in the manufacturing process **if all combined batches meet the approved in-process control limits**, the next step remains unaffected, and appropriate traceability is maintained.
- For **equipment used in aseptic manufacturing processes** (e.g., new filling line, new lyophilizer), **replacement of equipment with that of the same design and operating principle**, **when there is no change in the approved process methodology or in-process control limits**.

Manufacturing Process, Batch Size, and Equipment (Slide 2 of 2)

- **Addition of identical processing lines that operate parallel to each other** in the **drug substance and drug product manufacturing process** with no change in in-process control limits or product specification.
- For sterile drug products, **addition of, deletion of, or change in a reprocessing protocol for refiltrations** to control bioburden because of filter integrity test failures.
- **Decrease in the number of open handling steps or manual operation procedures**, when it reduces risk to product and there is no other change to the process (e.g., implementation of aseptic connection devices to replace flame protection procedures).
- For sterile drug products, **changes to the ranges of filtration process parameters** (such as **flow rate, pressure, time, or volume, but not pore size**) that are within currently validated parameters ranges and therefore would not warrant new validation studies for the new ranges.
- In the manufacture of sterile drug products, **change from a qualified sterilization chamber (ethylene oxide (EtO), autoclave) to another of the same design and operating principle** for the preparation of **container/closure systems, sterilization of "change parts" for processing equipment, and terminal sterilization of product**, when the new chamber and load configurations are validated to operate within the previously validated parameters. **This does not include situations that change the validation parameters.**

Specifications (Slide 1 of 2)

- **Addition of a new test to the specification for an excipient**.
- Change to the specification for a **drug substance, drug product, or pharmacopeial excipient** that is made **to comply with the official compendia if it is a change that does not relax an acceptance criterion or delete a test**.

  Specification changes not suitable for documentation in an annual report include changes to an assay, tests for impurities, degradation products, product-related substances, or biological activities that are approved in NDAs and ANDAs. Such changes should be submitted in a supplement.
- **Change in the approved analytical procedure** if the revised method maintains the original test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims to have or is represented to possess and **the acceptance criteria remain unchanged** [e.g., change in the flow rate or sample preparation for a high performance liquid chromatography (HPLC) method].
- **Replacement of a nonspecific identity test with a discriminating identity test** that includes a change in acceptance criteria (e.g., replacing *SDS-PAGE* with peptide map).

Specifications (Slide 2 of 2)

- Addition of an in-process test.
- **Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that ensures adequacy of mix**.
- **Revision of tablet hardness** (e.g., acceptance criterion for test result or change to a different analytical procedure and its associated acceptance criterion for test result) **if there is no change in the approved dissolution analytical procedure, criteria, or associated dissolution profile**.
- **Addition of a test for packaging material to provide increased assurance of quality**.
- **Tightening of an approved acceptance criterion** for a drug substance, a drug product, drug product formulation components, and in-process material.

Container/Closure System (Slide 1 of 2)

- **A change in the container/closure system for the storage of a nonsterile drug substance (solid, semisolid, or liquid)** when the proposed container/closure system has **no increased risk of leachable substances in the extractable profile** (for semisolids and liquids), and **equivalent protection properties** for the packaged material.
- **Use of or transfer to a contract manufacturing organization (CMO) for the washing, drying, or/and siliconization of a drug product stopper or any part of a container closure system**, provided the applicant certifies that the CMO's processes have been validated and the CMO's site has been audited and found CGMP compliant by the applicant (or by another party sponsored by the applicant).
- For **solid oral dosage forms**, when the **change is to use another suitable primary packaging component used in any other CDER-approved drug product**:
  - **Change in type of desiccant to another desiccant** that was previously used in another approved product and is suitable for its intended use.
  - **Elimination of a bottle filler**, such as a fibrous material (e.g., suitable type of cotton, rayon, polyester, etc.) that is used to fill empty or void space in the finished product container.

Container/Closure System (Slide 2 of 2)

- For parenteral drug products, **a change in glass supplier without a change in glass type or coating** and **without a change in container/closure dimension**s.
- **Changes to a crimp cap (ferrule and flip cap/overseal)**, provided that there are no changes to the color and that the container and closure integrity have been demonstrated using a validated test method. Note, however, that a change in the flip cap/overseal color to make it consistent with an established color coding system for that class of drug products is to be documented in an annual report.
- **Change to delete the company trademark or other markings on the crimp cap** (ferrule and flip cap/overseal) to comply with the official compendium.

Labeling Changes

- Revision in **drug product labeling to reflect the qualitative change in inactive ingredient(s) of coating formulation**, as recommended in the components and composition section of this guidance. The final Structured Product Labeling (SPL) reflecting the qualitative change should be submitted to the Agency when implementing this change to allow for maintenance of the current product information in eLIST **(**www.fda.gov/downloads/ForIndustry/DataStandards/StructuredProductLabeling/UCM164094.pdf**)**. This will help ensure the safe and effective use of the drug product.
- **A change in the drug product labeling to revise information related to CMC changes discussed in this guidance**. If the change involves associated revision of **drug product labeling**, the guidance mentioned in the above paragraph would apply.

Miscellaneous Changes

- **Extension of the drug substance retest dating period or drug product expiration dating period based on real-time stability data** from pilot-scale or larger/commercial-scale batches **following an approved stability protocol**.
- For immediate-release solid oral dosage forms, **if a dissolution test is performed**, **elimination of a test for identity or hardness from an approved stability protocol**.
- For **changes in an application that are fully consistent in scope and requirements with changes previously approved in a grouped supplement** (also defined as a Bundled Supplement), the same applicant can make the same change to similar drug products.
  (See CDER MAPP 5015.6, "Review of the Same Supplemental Change to More Than One NDA or ANDA in More Than One Review Division." January 2000;
  www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPolicies Procedures/ucm079567.pdf.

Appendix B:

Examples of Changes to be Documented in an Annual Report from

FDA's SUPAC-IR, SUPAC-MR, SUPAC-SS, and Changes to an Approved NDA or ANDA Guidance

Changes Submitted in Annual Reports

- **Components and Composition**
  - **Change to comply with the official compendium** except relaxation of an acceptance criterion or deletion of a test (see 21 CFR 314.70(c)(2)(iii)).
  - **Complete or partial deletion of an ingredient intended to affect only the color, flavor, or fragrance of the drug product without change in other approved specification**.
  - **Change in nonrelease controlling excipients**, expressed as percentage (w/w) of total formulation approved in the original application, as described in the SUPAC guidances.
  - **Change in the supplier of an excipient, where the technical grade and specification for the excipient remain the same**.
  - **Changes in release controlling excipients less than or equal to 5% expressed as a w/w percentage of total release controlling excipients approved in the original application of a MR solid oral dosage form**. After the change, the total weight of the dosage form and its specification would remain the same as originally approved.

Manufacturing Site

When the new site has a satisfactory CGMP inspection status for the type of operation involved, the following changes can be documented in an annual report:

- **A move to a different manufacturing site for secondary packaging, labeling, ink imprinting on a solid oral dosage form**, and **manufacture or processing of drug substance intermediates other than the final intermediate**.

- **Change in location of manufacturing** (including terminal sterilization of finished product) **within the same facility or site for both company owned and contract manufacturers** that do not include any scale-up changes, changes in manufacturing process or equipment, or changes in components and composition of drug product. The standard operating procedures, personnel with suitable experience with the manufacturing processes, environmental conditions and controls, and manufacturing batch records will remain the same except for administrative information and the location within the same facility or site.

Manufacturing Process

- For drug products, change to equipment of the same design and operating principles, capacity, and/or batch size (increase or decrease), except for natural protein drug substances and natural protein drug products.

- Change in the order of addition of drug product components for solution dosage forms (except active pharmaceutical ingredients), or change in the order of ingredients added to solutions used in unit operations (e.g., granulation solutions).

Specifications

- **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.**

- 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.

Summary

- Discussed the Background and Final Guidance
- Assessment of effect of change(s) on product quality through appropriate studies and tests; their documentation, and submission of Postapproval CMC Changes to Drug Applications
  - Major Changes: Prior Approval Supplements
  - Moderate Changes: CBE-30 and CBE-0 Supplements
  - **Minor Changes: Annual Reports**
- Examples of Postapproval Manufacturing Changes listed in Appendix A and B of the Guidance to be documented in Annual Reports if they have a minimal potential to have an adverse effect on approved drug product quality

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  Acting Director, Office of Pharmaceutical Science, CDER

Presenter's Contact Information

- **Rajendra.Uppoor@fda.hhs.gov**
  (301) 796-1618

  FDA/CDER/OPS/PARS, HFD-003
  Building 51, Room 4174
  10903 New Hampshire Ave
  Silver spring, MD 20993-0002

Questions

- Additional questions can be sent to CDER Small Business and Industry Assistance (CDER SBIA) at:
- E: **CDERSBIA@fda.hhs.gov**
- P: 1-866-405-5367 | 301-796-6706