CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Michail Alterman 240-402-9355, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

August 2017
Pharmaceutical Quality/CMC

CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

August 2017
Pharmaceutical Quality/CMC

TABLE OF CONTENTS

CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to holders of biologics license applications (BLAs) for specified products regarding the types of changes to an approved BLA to be documented in an annual report under 21 CFR 601.12. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we (FDA or Agency) generally consider to have a minimal potential to have an adverse effect on product quality.[2] Under FDA regulations, postapproval changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a *minimal potential* to have an adverse effect on product quality must be documented by applicants in an annual report.[3]

This guidance applies to all of the specified categories of biological products in 21 CFR 601.2(a). The guidance does not apply to blood-derived products, in vitro diagnostics, cellular and gene therapy products, and vaccines and related products[4]; however, a BLA holder for any other naturally derived biological product should discuss with FDA whether the recommendations in this guidance apply to his or her BLA.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] In this guidance, the term *product quality* refers to the "identity, strength, quality, purity, or potency of the product as [these factors] may relate to the safety or effectiveness" of the biological product (21 CFR 601.12(d)(1)).

[3] See 21 CFR 601.12(d).

[4] For a description of these product classes, see guidance for industry *Changes to an Approved Application: Biological Products*. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or the FDA Biologics guidance Web page at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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 the Agency of a change to an approved BLA in accordance with all statutory and regulatory requirements—including section 506A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356a) and 21 CFR 601.12. Section 506A of the FD&C Act provides requirements for making and reporting manufacturing changes to an approved application or license and for distributing a drug product made with such changes. Under 21 CFR 601.12, each postapproval change in the product, production process, quality controls, equipment, facilities, or responsible personnel established in the approved BLA must be reported using the submission type associated with one of three reporting categories: major, moderate, or minor. In addition to complying with the requirements in section 506A of the FD&C Act and 21 CFR 601.12, applicants are required to comply with other applicable laws and regulations, including CGMP regulations in 21 CFR parts 210 and 211.

If a change is considered to be major, an applicant must submit and receive FDA approval of a supplement to the BLA before the product produced with the manufacturing change is distributed (also known as a prior approval supplement (PAS)). If a change is considered to be moderate, an applicant must submit a supplement at least 30 days before the product is distributed (CBE-30 supplement) or, in some cases, the product may be distributed immediately upon FDA's receipt of the supplement (CBE-0 supplement).[5] If a change is considered to be minor, an applicant may proceed with the change but must notify FDA of the change in an annual report. For any change, applicants must assess the effects of the change on product quality through appropriate studies.[6] For additional background information regarding the reporting categories for BLAs, see the guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*.

In our September 2004 final report, *Pharmaceutical CGMPs [Current Good Manufacturing Practices] 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, the Agency determined that to provide the most effective public health protection, our CMC regulatory review should be based on an understanding of product risk and how best to manage this risk.

[5] *CBE* is *changes being effected*.

[6] 21 CFR 601.12(a)(2).

III. RECOMMENDATIONS FOR REPORTING CERTAIN CHANGES IN AN ANNUAL REPORT

The number of CMC manufacturing supplements for BLAs 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 postapproval manufacturing supplements and determined that certain changes being reported generally present minimal risk to the quality of the product. Thus, FDA has determined that it would be appropriate to issue guidance to recommend that certain changes, listed in the Appendix, generally should be documented in an annual report.

The changes listed in the Appendix are categorized according to the type of manufacturing change. These changes are either additions or revisions to the CMC changes considered by FDA to be appropriate for reporting in an annual report that were previously published in the guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products.*

Thus, before submitting a supplement based on the guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, an applicant should also refer to the list of risk-based recommendations that are provided in the Appendix of this guidance. These recommendations are intended to help clarify whether submission of a supplement or documentation of the change in an annual report may be appropriate.

FDA recommends that the changes listed in the Appendix generally should be submitted in an annual report. However, if a BLA holder is planning to make a change that is listed in the Appendix, the BLA holder should evaluate the change in the context of the holder's particular circumstances to determine whether the proposed change would present a minimal potential to have an adverse effect on product quality and therefore would be appropriately documented in an annual report. BLA holders may, based on their specific circumstances, determine that a change described in the Appendix would appropriately be submitted as a supplement rather than in an annual report. If FDA disagrees with the categorization, FDA may notify the applicant of the correct category and request additional information.

To the extent that a recommendation in this guidance to document a single change in an annual report is found to be inconsistent with a previously published FDA guidance, the recommendations in this guidance would apply. For changes not listed in the Appendix, or if multiple related changes being implemented simultaneously increases the potential to have an adverse effect on product quality, applicants should refer to other CDER and CBER guidances to determine the appropriate reporting category (i.e., PAS, CBE-30, CBE-0, or annual report) for notifying the Agency of the changes.

All changes to an approved product or process, regardless of the reporting mechanism, should be evaluated, approved by the quality unit,[7] and implemented using a robust change

[7] In this guidance, the term *quality unit* is synonymous with the term *quality control unit* as described in 21 CFR 210.3.

management system within the pharmaceutical quality system, using risk management approaches as outlined in the International Council for Harmonisation (ICH) guidance for industry *Q9 Quality Risk Management* and product-specific knowledge management. Applicants should note the recommendations regarding change control for active pharmaceutical ingredient manufacturing that are provided in the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients.* CGMP regulations for finished pharmaceuticals also 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. The activities addressed in FDA's CGMP regulations include establishing and following appropriate written procedures reviewed and approved by the quality unit, qualifying equipment as suitable for its intended use, using validated test methods, and ensuring the manufacturing process's ongoing state of control (which should include continued process verification and stability studies depending on the nature of the change).[8]

For specific questions associated with whether the change should be submitted to the Agency in a supplement or documented in an annual report, we recommend that applicants contact the Office of Pharmaceutical Quality in CDER or the Office of Communication, Outreach and Development in CBER.

IV. CONTENTS OF ANNUAL REPORT NOTIFICATION

To document changes in an annual report in accordance with 21 CFR 601.12(d), the applicant must include the following information for each change[9]:

- A full description of the CMC changes, including:
  - The manufacturing sites or areas involved.
  - The date the change was made.
  - A cross-reference to relevant validation protocols and/or standard operating procedures.
  - Relevant data from studies and tests performed to assess the effect of the change on product quality.
- A list of all products involved.
- A statement that the effects of the change have been assessed.

The applicant should describe each change in an annual report in enough detail to allow the Agency to evaluate the change and determine whether the appropriate reporting category has

[8] See 21 CFR parts 210 and 211.

[9] 21 CFR 601.12(d)(3) describes the information for each change that must be contained in the annual report.

been used.[10] If the submitted change is inappropriate for documentation in an annual report, FDA may notify the applicant of the correct category and may request additional information. However, inappropriate documentation should be uncommon because applicants should only use this mechanism of reporting a change when they are confident that documentation in an annual report is appropriate.

[10] Under 21 CFR part 211, manufacturers are required to retain certain records, including records related to batch production and control, and to make those records readily available for inspection during the retention period. Other documentation and data that support reporting the change in an annual report should also be retained and made available to the Agency on request (e.g., during an inspection).

APPENDIX: EXAMPLES OF CMC POSTAPPROVAL MANUFACTURING CHANGES THAT FDA GENERALLY CONSIDERS TO HAVE A MINIMAL POTENTIAL TO HAVE AN ADVERSE EFFECT ON PRODUCT QUALITY

1. Components and Composition

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

2. Manufacturing Sites

    2.1. Site change for testing. This includes sites for testing of lower risk process-related impurities (e.g., host cell proteins, host cell DNA, residual solvents) when the method was successfully validated at the new site and the new site, where applicable, meets relevant CGMP requirements for the type of operation involved (e.g., no outstanding FDA warning letters or "official action indicated" compliance status). This does not include sites for testing for conformance to quality control specifications, including potency, impurities (except those that are lower risk), and safety testing (e.g., sterility and virus testing).

    2.2. Site change for labeling or secondary packaging when the new site has a satisfactory CGMP status.

    2.3. Change in the location of manufacturing steps within a manufacturing area that is already listed in an approved BLA where those steps are part of a nonsterile drug substance production process and the new location will have no impact or will lower the risk of contamination or cross-contamination (e.g., improved air classification, better process flow, enhanced segregation of pre- and post-viral inactivation steps).

    2.4. Modification of a manufacturing facility listed in an approved BLA that does not increase the risk of contamination (e.g., affect sterility assurance) or otherwise present a meaningful risk of affecting product quality.

    2.5. Manufacture of an additional drug product (already licensed or an investigational product), in a multiple-product area listed in an approved BLA that is producing other products, if:

        2.5.1. Specific identity tests exist to differentiate between all products manufactured at the facility; and

        2.5.2. Change-over procedure between manufacturing processes does not require new changes in cleaning procedures; and

        2.5.3. 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 (e.g., botulinum toxin), highly immunogenic or allergenic products (e.g., penicillin), products that can accelerate degradation of another product (e.g., proteases), 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, Batch Size, and Equipment[11]

3.1. Changes in mixing times for solution dosage forms.

3.2. Small changes in the size 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 process parameter ranges for the next step remain unaffected.

3.3. Changes to batch sizes that do not involve use of different equipment (e.g., increase in roller bottle number, minor increases in fermentor volume, or minor increases in load volumes for chromatography columns).

3.4. Addition of an identical duplicate process chain or unit process in the drug substance and drug product manufacturing process with no change to equipment, process methodology, in-process control limits, process parameter ranges, or product specifications, with the exception of addition of major equipment used in aseptic processing (e.g., new filling line, new lyophilizer).

3.5. Reduction of open-handling steps if there is a reduction in product exposure that represents improvement in the assurance of product protection (e.g., implementation of sterilize-in-place connections to replace aseptic connections, automated weight checks, installation of a barrier to protect product, replacement of a manual stopper recharging step with an automated recharging step).

3.6. For sterile drug products, change from a qualified sterilization chamber (ethylene oxide, autoclave) to another of the same design and operating principle for containers/closures 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 tests and acceptance criteria to specification for approved excipients.

4.2. Change to a drug substance or drug product to comply with an official compendial test, except for changes to assays, impurities, product-related substances, or biological activities or changes described in 21 CFR 601.12(c)(2)(iv).

[11] FDA generally considers these changes to have a minimal potential to have an adverse effect on product quality only when they are implemented in licensed areas for the same type of operation or testing and/or dosage form.

4.3. Change in the regulatory analytical procedure if the acceptance criteria remain unchanged and the revised method maintains basic test methodology (e.g., change in the flow rate or sample preparation for an HPLC[12] method) 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.

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[13] with peptide mapping).

4.5. Addition of an in-process test.

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

4.7 Tightening of an existing acceptance criterion.

5. Container Closure System

5.1. 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 (based on the extractables and/or leachables profile and whether stability data are consistent with historical trends), and the new container offers equivalent or greater protection properties from air and moisture.

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

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

[12] *HPLC* stands for high-performance liquid chromatography.

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