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

Guidance for Industry

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)

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Contains Nonbinding Recommendations

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

This guidance represents 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 office 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 biological 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 FDA generally considers 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 biological products, as defined in 21 CFR 600.3(h), that fall under one of the following categories specified in 21 CFR 601.2(a): therapeutic DNA plasmid products, therapeutic synthetic peptide products of 40 or fewer amino acids, monoclonal antibody products for in vivo use, and therapeutic recombinant DNA-derived products.[4] It also applies to combination products licensed under a BLA, where the biological product constituent part falls under one of these categories specified in 21 CFR 601.2(a). The guidance does not apply to blood or blood components, blood-derived products, in vitro diagnostics, cellular and gene therapy products, or vaccines and related products[5]; however, a BLA holder for any other

[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] Only a product that meets the definition of *biological product* can fall within the specified categories of biological products described in 21 CFR 601.2(a).

[5] For recommendations related to these products, see guidances for industry *Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture* (December 2014) and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

naturally derived biological product should discuss with FDA whether the recommendations in this guidance apply to his or her BLA.

This guidance focuses on reporting mechanisms. For information about change management within the pharmaceutical quality system, see International Council for Harmonisation (ICH) guidances for industry *Q9 Quality Risk Management* (June 2006), *Q10 Pharmaceutical Quality System* (April 2009), and *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

An applicant must notify FDA 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.[6] 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 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.[7]

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)).[8] If a change is considered to be

[6] Applicants must also comply with other applicable laws and regulations, including current good manufacturing practice (CGMP) regulations in 21 CFR parts 210 and 211, as well as the applicable requirements in 21 CFR parts 600 through 680. CGMP regulations cover activities such as establishing and following appropriate written procedures reviewed and approved by the quality control unit, qualifying equipment as suitable for its intended use, using validated test methods, and ensuring the manufacturing process's ongoing state of control (which may include additional stability studies depending on the nature of the change).

[7] The ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) outlines terminologies and concepts, including *established conditions*, that may impact how an applicant reports postapproval CMC changes. FDA considers established conditions to include the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product, and that can be specifically identified and proposed by the sponsor and approved as part of a BLA. Changes to the established conditions must be reported to FDA (21 CFR 601.12). CMC information in an application that is not considered an established condition may be changed postapproval without the submission of a supplement or documentation in an annual report.

[8] 21 CFR 601.12(b).

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).[9] 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.[10] For any change, applicants must assess the effects of the change on product quality through appropriate validation and/or other studies.[11] 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* (July 1997).

The number of CMC manufacturing supplements for BLAs has increased over the last several years. In keeping with a risk-based approach to CMC review,[12] FDA has 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 (i.e., they generally have minimal potential to have an adverse effect on product quality).

III. RECOMMENDATIONS FOR REPORTING CERTAIN CHANGES IN AN ANNUAL REPORT

Examples of changes that have minimal potential to have an adverse effect on product quality and therefore must be submitted in an annual report are found in 21 CFR 601.12(d). Additionally, FDA provides examples in the Appendix of changes that it generally considers to have a minimal potential to have an adverse effect on product quality, which are categorized according to the type of manufacturing change. 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 generally intends to notify the applicant of the correct category and may request additional information.

The examples of changes in the Appendix include modified versions of relevant CMC changes included 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 examples listed in the Appendix of this guidance, which are intended to help clarify whether submission of a supplement or documentation of the change in an annual report may be appropriate.

When considering the correct reporting category for a submission, the applicant should ensure that the highest risk change determines the reporting category that is chosen for the submission.

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[9] 21 CFR 601.12(c). *CBE* is *changes being effected*.

[10] 21 CFR 601.12(d).

[11] 21 CFR 601.12(a)(2).

[12] See FDA's *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach* (September 2004).

For example, there may be several minor-risk changes associated with one major-risk change, in which case the reporting category for the major-risk change should define the appropriate submission type (i.e., PAS).

If unsure whether a change should be submitted to FDA in a supplement or documented in an annual report,[13] applicants should 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[14]:

- A full description of the CMC change, 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 FDA to evaluate the change and determine whether the appropriate reporting category has been used.[15] If the submitted change is inappropriate for documentation in an annual report, FDA generally intends to notify the applicant of the correct category and may request additional information. However, applicants should only use this mechanism of reporting a change when they are confident that documentation in an annual report is appropriate.

[13] For example, the change is not listed in the Appendix, or multiple related changes being implemented simultaneously increases the potential to have an adverse effect on product quality.

[14] 21 CFR 601.12(d)(3) describes the information for each change that must be contained in the annual report.

[15] 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 FDA on request (e.g., during an inspection or in responding to a request for information in advance or in lieu of an inspection, in accordance with section 704(a)(4) of the FD&C Act).

APPENDIX: CHANGES THAT FDA GENERALLY CONSIDERS HAVING A MINIMAL POTENTIAL TO HAVE AN ADVERSE EFFECT ON PRODUCT QUALITY

This appendix provides examples of chemistry, manufacturing, and controls postapproval manufacturing changes that FDA generally considers having a minimal potential to have an adverse effect on product quality. Changes that have a minimal potential to have an adverse effect on product quality must be submitted in an annual report in accordance with 21 CFR 601.12(d).

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[1]

    2.1. Site change for testing. This includes:

    - Testing of process-related impurities whose risk has been mitigated (e.g., residual solvents) when the method has been successfully validated at the new site.
    - Compendial methods that are of low complexity (e.g., pH, osmolality).

    This does not include:

    - Testing for conformance to quality control specifications, including potency and impurities (except those whose risk has been mitigated, such as residual solvents).
    - Testing for quality attributes for which the robustness of the analytical method may be critical (e.g., sterility and virus testing) unless the new site is registered with and has been inspected by FDA for the type of testing being transferred and the methods and specifications for testing quality attributes are the same as for the original testing site.

    2.2. Site change for labeling or secondary packaging.

    2.3. Change in the location of manufacturing steps within a manufacturing area that is already listed in an approved biologics license application (BLA) where those steps are

[1] Manufacturing site changes that are submitted in annual reports should only be effected in facilities that meet current good manufacturing practice (CGMP) requirements. Where FDA's current classification is "official action indicated," the facility is considered to be in an unacceptable state of compliance with regard to CGMP requirements. FDA posts inspection classification decisions in a publicly available database updated every 30 days; see Inspection Classification Database at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database. Applicants should consider the status in the database and request and use information from the proposed new manufacturing site if more current than that posted by FDA.

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. Introduction of an additional drug product in a multiple-product area, or a multiple-product contract manufacturing site, that is listed in an approved BLA and producing other products, if:

- Specific identity tests exist to prevent cross-contamination and other errors;[2] and
- Changeover procedure between manufacturing processes does not require new changes in cleaning procedures; and
- 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[3]

3.1. Manufacturing batch size or scale change caused by minor 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.

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

3.3. 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

[2] In multiple-product contract manufacturing sites, if the identity tests are qualitative in nature, they should be specific to the additional product in its designated labeling and packaging configuration and should distinguish that product from others being processed at the same site (e.g., labeling and packaging configuration may be part of the identity testing of the product but should not be the standalone identity test).

[3] 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.

specifications, with the exception of addition of major equipment used in aseptic processing (e.g., new aseptic filling line, new lyophilizer).

3.4. 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).

3.5. For sterile drug products, change from a qualified sterilization chamber (e.g., ethylene oxide, autoclave) to another of the same design and operating principle for preparation of the container closure system when the new chamber and load configurations are validated to operate within the previously validated parameters.

3.6. For sterile drug products, changes to the ranges of filtration process parameters (such as flow rate, pressure, time, or volume, but not filter pore size) that are within previously validated 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 described in 21 CFR 601.12(c)(2)(iv).

4.3. Change in the analytical procedure described in the approved application if the acceptance criteria remain unchanged and the revised method maintains basic test methodology (e.g., change in the flow rate or change in the sample preparation for an HPLC[4] 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.[5]

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[6] 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.

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

[5] See 21 CFR 601.12(d)(2)(vii).

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

4.8. Extension of the drug substance retest dating period or drug product expiration dating period based on full shelf-life stability data following an approved stability protocol.

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 (e.g., from air, moisture, and light (for light-sensitive products)).

5.2. Use of a contract manufacturing organization to wash the drug product's container closure system in accordance with the original acceptance criteria for the washing process.

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.