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

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)

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

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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. 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.

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; 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

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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.
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). 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. 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.

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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, 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 change9:

- 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

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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. 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

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\textsuperscript{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\textsuperscript{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.

\textsuperscript{12} HPLC stands for high-performance liquid chromatography.

\textsuperscript{13} SDS-PAGE stands for sodium dodecyl sulphate polyacrylamide gel electrophoresis.