
Changes to Disposable Manufacturing Materials: Questions and Answers 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)
Center for Veterinary Medicine (CVM)**

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Pharmaceutical Quality/Manufacturing Standards

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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	DISCUSSION	2
III.	QUESTIONS AND ANSWERS.....	3
	<i>Q1: What are some possible changes an applicant can make to disposable manufacturing materials and what reporting categories are applicable?</i>	<i>3</i>
	<i>Q2: Are there steps to lower the reporting category of a supplement?</i>	<i>4</i>
	<i>Q3: When and how should an applicant contact FDA for feedback on a proposed change?</i>	<i>5</i>
	APPENDIX A	7
	APPENDIX B	9

Changes to Disposable Manufacturing Materials: Questions and Answers Guidance for Industry¹

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 describes chemistry, manufacturing, and controls (CMC) postapproval changes related to disposable manufacturing materials² that applicants can pursue in drug and biological product manufacturing. This guidance applies to biologics license application (BLA) products licensed under section 351(a) or 351(k) of the Public Health Service Act (PHS Act); human drug products marketed as new drug applications (NDAs) or abbreviated new drug applications (ANDAs) under section 505(b)(1), 505(b)(2), or 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); and animal drugs marketed as new animal drug applications (NADAs) or abbreviated new animal drug applications (ANADAs) under section 512(b)(1) or 512(b)(2) of the FD&C Act.³ This guidance applies to all manufacturing establishments, including those that perform functions under contract as defined in the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (November 2016).⁴

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

¹ This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM). You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at <https://www.regulations.gov/docket?D=FDA-2017-D-6821>). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

² For the purposes of this guidance, disposable manufacturing materials include, but are not limited to, single-use system assemblies and parts, filters, mixing bags, bioreactor bags, and tubing.

³ This guidance also applies to combination products with device constituent parts that are the subject of BLAs, NDAs, ANDAs, and application supplements.

⁴ 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>.

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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. DISCUSSION

FDA receives questions about the limited availability of disposable manufacturing materials during periods of increased demand (e.g., public health emergencies or natural disasters). Limited availability of disposable manufacturing materials can affect sterile drugs and biological products. Applicants should use science-based and risk-based principles, and refer to current guidances for industry, to determine the appropriate reporting category to communicate changes to disposable manufacturing materials.

FDA expects all changes to be appropriately managed by an establishment's pharmaceutical quality system under the statutory requirements in section 501(a)(2)(B) of the FD&C Act and applicable current good manufacturing practice (CGMP) regulations in 21 CFR parts 210, 211, and 600-680, and part 4 for combination products. Additionally, applicants should follow the principles described in FDA's ICH guidances for industry: *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016), *Q9 Quality Risk Management* (June 2006), *Q10 Pharmaceutical Quality System* (April 2009), and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

Changes to disposable manufacturing materials for application products should be communicated to FDA through postapproval submissions — such as prior approval supplements (PAS) or changes being effected (CBE) supplements — or in annual reports.^{5, 6, 7, 8, 9, 10, 11} Regulations describe types of postapproval changes and associated reporting categories.¹² Under CGMP, any changes to disposable manufacturing materials should be documented within the pharmaceutical

⁵ Guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021).

⁶ Guidance for industry *CMC Postapproval Manufacturing Changes for Specified Biological Products to Be Documented in Annual Reports* (December 2021).

⁷ Guidance for industry *CMC Postapproval Manufacturing Changes to Be Documented in Annual Reports* (March 2014).

⁸ Guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved NADA/ANADA* (May 2007).

⁹ Guidance for industry *Changes to an Approved NDA or ANDA* (April 2004).

¹⁰ Guidance for industry *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997).

¹¹ FDA ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

¹² See 21 CFR §§ 314.70, 314.97, 514.8, and 601.12.

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quality system¹³ and available upon request during an inspection, including when the element being changed is not specifically described in an application. Changes to drug products for administration to humans or animals must be approved by the quality unit.¹⁴

Changes to disposable manufacturing materials for nonapplication products, including nonprescription drug products, should be documented under the pharmaceutical quality system¹⁵ and must be approved by the quality unit.¹⁶

III. QUESTIONS AND ANSWERS

The following questions and answers provide information about making changes to disposable manufacturing materials.

Q1: What are some possible changes an applicant can make to disposable manufacturing materials and what reporting categories are applicable?

A1: Changes to disposable manufacturing materials can include, but are not limited to, the following: (1) changing suppliers, with or without a change in product-contacting material; (2) using similar materials that differ in composition or design; (3) reducing the number of materials used or extending the use of materials in manufacturing by increasing throughput; and (4) reusing a disposable manufacturing material. Current guidances for industry provide examples of relevant changes and corresponding reporting categories.¹⁷ Refer to Appendix A and Appendix B of this guidance for a summary of examples. These examples are not intended to be comprehensive.

Factors to be considered when assessing risks to product quality and determining the reporting category for the change include the following: (1) intended use of the disposable manufacturing material in the manufacturing process; (2) whether a disposable manufacturing material is used upstream or downstream; (3) use of redundant steps within the manufacturing process; (4) enhanced product and process knowledge gained since application approval; (5) whether in-process and release/stability controls meet current regulations for detecting differences in product quality attributes; and (6) the extent of existing validation data.

For approved BLAs, NDAs, ANDAs, NADAs, and ANADAs, applicants should consider factors such as those described above to determine the potential scope and risk to product quality of the proposed change (i.e., major, moderate, or minor), considering the specific

¹³ FDA ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

¹⁴ 21 CFR 211.22

¹⁵ See footnote 13.

¹⁶ See footnote 14.

¹⁷ See footnotes 5-11.

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product and/or process affected by the change to disposable manufacturing material. The outcome of this assessment, in conjunction with regulations and guidances for CMC changes, can help determine which reporting category is appropriate for a proposed change. Changes that require an application supplement should be filed at the appropriate reporting category, commensurate with the level of risk to product quality. Additionally, as described in the FDA ICH guidance for industry *Q9 Quality Risk Management* (June 2006), the robustness of the data submitted in support of such a supplement should be commensurate with the level of risk to product and process. For a description of major, moderate, and minor changes, see 21 CFR §§ 601.12 (BLAs), 314.70 (NDAs), 314.97 (ANDAs), and 314.8 (NADAs and ANADAs). For elaboration on the potential risk to product quality for different changes to disposable manufacturing materials, including high-risk changes that could potentially affect critical quality attributes such as product sterility, see Appendix A and Appendix B of this guidance. Applicants should review the FDA ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021) and the draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021)¹⁸ for risk-based tools to facilitate streamlined change implementation.

Q2: Are there steps to lower the reporting category of a supplement?

A2: A comparability protocol (CP) could be used as a tool for making changes to disposable manufacturing materials because a change to one material can be implemented to many products. As described in the guidance for industry *Comparability Protocols – Chemistry, Manufacturing, and Controls Information for New Animal Drugs* (April 2016) and draft guidance for industry *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016),¹⁹ a CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC postapproval change on the identity, strength, quality, purity, or potency of a drug product or a biological product.²⁰

Applicants can use a CP to obtain feedback from FDA on prospective scientific approaches submitted as part of an original application or PAS to facilitate expeditious implementation of postapproval changes. CPs allow FDA to review a description of one or more proposed CMC postapproval changes covering approved products at one or more manufacturing establishments, supporting information (including any developmental batch data, analysis and risk assessment activities), the plan for implementing the change(s), and, if appropriate, a proposed reduced reporting category. If the original application or PAS containing the CP is approved, the change can be implemented under a lower reporting category than would

¹⁸ When final, this guidance will represent the FDA’s current thinking on this topic.

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²⁰ Additional information specific to biological products can be found in the FDA ICH guidance for industry *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (June 2005).

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ordinarily be expected based on current guidances for industry (e.g., changes otherwise requiring a PAS could be implemented under a CBE-30).

An approved CP can be used for a one-time change or be used repeatedly for a specified type of change over the lifecycle of a product. A CP can also be submitted to cover an identical change that affects multiple applications (e.g., grouped supplements, trans-BLA submissions). A CP is the same as a Postapproval Change Management Protocol as described in the FDA ICH guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021).

The use of CPs can be limited for certain changes (e.g., major changes), where a reduced reporting category is not adequate or appropriate to ensure product quality and patient safety. Examples of such circumstances include insufficient understanding of the effect of the change on the product or process; when the CGMP compliance status of an establishment at the time of change impacts the reporting category; or whether data from nonclinical safety, pharmacokinetic/pharmacodynamic, or safety and efficacy studies are needed to evaluate the effect of changes on product quality. Even if a reduced reporting category is not justified, FDA can implement flexible assessment practices, such as expediting assessment of supplements, when warranted.^{21, 22, 23, 24}

Q3: When and how should an applicant contact FDA for feedback on a proposed change?

A3: Applicants should review existing regulations and guidances for industry to determine the appropriate reporting category for a proposed change. Because the examples in guidances are not comprehensive and may not address novel situations, applicants should contact FDA for feedback on a proposed change, especially before submitting a supplement with a lower reporting category than what is required in existing regulations or recommended in existing guidance. FDA intends to provide timely assessment of and feedback on these types of proposed changes to meet urgent public health needs.

²¹ For FDA policies describing expedited review requests related to prior approval supplements for NDAs and BLAs, see 21 CFR 314.70(b)(4) and 601.12(b)(4). See also CDER Manual of Policies and Procedures (MAPP) 5310.3 Rev. 2: *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes* (April 2021).

²² For FDA policies describing expedited review requests related to prior approval supplements for NADAs and ANADAs, see CVM Program Policy and Procedures Manual 1243.3020: *Review of Submissions in the Submission Tracking and Reporting System (STARS) Queue* (May 2021).

²³ For FDA policies on drug shortage management, see CDER MAPP 4190.1 Rev. 3: *Drug Shortage Management* (November 2018), and CBER SOPP 8506, *Management of Shortages of CBER-Regulated Products* (February 2022).

²⁴ For FDA policies describing prioritization of the review related to original ANDAs, amendments, and supplements thereof, see MAPP 5240.3 Rev. 5: *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (January 2020).

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When contacting FDA about initiating changes to disposable manufacturing materials, the applicant should be ready to provide relevant information, including: (1) any affected products and processes; (2) proposed changes to mitigate effects of the component shortage on product quality and supply; (3) involvement of other products and/or manufacturing establishments (including contract manufacturing organizations); and (4) any information related to potential or actual drug shortage concerns. BLA, NDA, NADA, and ANADA applicants who want to request a meeting with FDA to discuss a particular product or application should contact the appropriate review team.²⁵

²⁵ For additional questions, contact the appropriate product center: CDER at CDER-OPQ-Inquiries@fda.hhs.gov or CVM at AskCVM@fda.hhs.gov. For CBER-regulated products, applicants should contact the appropriate CBER review office. If a regulated product could enter or is currently in drug shortage, the applicant should also communicate with drugshortages@fda.hhs.gov (for products regulated by CDER), cbershortage@fda.hhs.gov (for products regulated by CBER), or animaldrugshortages@fda.hhs.gov (for products regulated by CVM).

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APPENDIX A

The following are examples of potentially relevant changes¹ and corresponding reporting categories for a new drug application (NDA), abbreviated new drug application (ANDA), new animal drug application (NADA), and abbreviated new animal drug application (ANADA) products. Note: this does not include biologics license application (BLA) products. These examples come from the following guidances for industry: *Changes to an Approved NDA or ANDA: Questions and Answers* (January 2001), *Changes to an Approved NDA or ANDA* (April 2004), *Chemistry, Manufacturing and Controls Changes to Approved NADA/ANADA* (May 2007), and *CMC Postapproval Manufacturing Changes to be Documented in Annual Reports* (March 2014).

Prior Approval Supplement:

- Change from sterile filtration to moist heat sterilization for products containing heat-stable active pharmaceutical ingredients.
- Deletion or substitution of a filtration step in an aseptic processing operation.
- Change to a product contact component in an aseptic filling line from a disposable plastic component to a reusable stainless-steel component.
- Changes to the pore size rating of a filter used in aseptic processing.

Changes Being Effected (CBE):

CBE-30:

- Increase of the flow rate filtration parameter for aseptic processing without a change to the filter materials or pore size rating.
- Reduction of the number of redundant sterilizing filters in series for repeated filtration of a bulk.
- Increase in the bulk solution storage time for a terminally sterilized drug product by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

CBE-0:

- Elimination of an in-process filtration step for a terminally sterilized drug product.

¹ For the examples listed in Appendix A, the term “change” refers to a change in a disposable manufacturing material or a change to a manufacturing process or process parameter that reduces the amount of a disposable manufacturing material needed to complete that process.

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43 **Annual Report:**

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45 • Within a currently validated process parameter range, a change in the range of filtration
46 volume for a sterile drug product.

47

48 • Increase in the bulk solution storage time for a terminally sterilized drug product by no
49 more than 50 percent beyond the validated limits in the approved application when
50 bioburden limits are unchanged.

51

52 • Deletion of a reprocessing protocol for refiltrations of a sterile drug product to control
53 bioburden because of filter integrity test failures.

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APPENDIX B

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57 The following are examples of potentially relevant changes¹ and corresponding reporting
58 categories for biologics license application (BLA) products. Note: this does not include new drug
59 application (NDA), abbreviated new drug application (ANDA), new animal drug application
60 (NADA), and abbreviated new animal drug application (ANADA) products. These examples
61 come from the following guidances for industry: *Changes to an Approved Application for*
62 *Specified Biotechnology and Specified Synthetic Biological Products* (July 1997), *Changes to an*
63 *Approved Application: Biological Products* (July 1997), *CMC Postapproval Manufacturing*
64 *Changes for Specified Biological Products to be Documented in Annual Reports* (December
65 2021), and *Chemistry, Manufacturing and Controls Changes to an Approved Application:*
66 *Certain Biological Products* (December 2017).

67 68 **Prior Approval Supplement:**

69
70 *Drug substance:*

- 71
- 72 • Change from a stainless-steel to disposable (e.g., bag) bioreactor or vice versa.
- 73
- 74 • Increase in the number of cycles of resin and membrane re-use without an approved
- 75 protocol.
- 76
- 77 • New or revised purification process (e.g., change in the resin or filter material, loading
- 78 scale, column size, or elution rate of a chromatographic column).
- 79
- 80 • Change in the method(s) for virus or adventitious agent removal or inactivation.

81
82 *Drug product:*

- 83
- 84 • Addition, deletion, or substitution of unit operation(s) or change in their sequence.
- 85
- 86 • Change in scale of the manufacturing process.
- 87
- 88 • Changes that affect product sterility assurance, such as changes in product or component
- 89 sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic
- 90 processing operation.
- 91
- 92 • Change in a membrane material or dimensions of the final sterilization filter.

93 94 **Changes Being Effectuated (CBE):**

95
96 CBE-30:

¹ For the examples listed in Appendix B, the term “change” refers to a change in a disposable manufacturing material or a change to a manufacturing process or process parameter that reduces the amount of a disposable manufacturing material needed to complete that process.

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98 *Drug substance:*

99

- 100 • Change in the filter or resin supplier with no change in the resin material, operating or
101 performance parameters.

102

103 *Drug Product:*

104

- 105 • Replacement of equipment with that of similar, but not identical, design and operating
106 principle that does not affect the process methodology, process operating parameters or
107 aseptic processing.

108

- 109 • Change to a final sterilization filter supplier with no change in material, dimensions, or
110 sterilization method.

111

- 112 • Changes to sterilization cycles for sterile product contact equipment.

113

114 **Annual Report:**

115

- 116 • Addition or replacement of equipment of the same size and material of construction used
117 in harvesting and pooling with no change in the process parameters specified in the
118 approved BLA.

119

120