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COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers

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Guidance for Industry

March 2021

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)

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders and the FDA web page titled "Search for FDA Guidance Documents," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an email request to druginfo@fda.hhs.gov or ocod@fda.hhs.gov to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact (CDER) CDER-OPQ-Inquiries@fda.hhs.gov or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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Guidance for Industry

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to collate recommendations for appropriate reporting category and the content of postapproval change submissions across numerous FDA guidance documents. This guidance conveys recommendations to holders of approved new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs) regarding the reporting and implementation of some common changes to container closure system (CCS) components consisting of glass vials and stoppers for approved[1] sterile drug products, including biological products, administered parenterally. This guidance also discusses pathways available to application holders to obtain Agency feedback. Additionally, this guidance discusses risk-based tools available to facilitate the implementation of changes to CCSs consisting of glass vials and stoppers. This guidance does not apply to CCS types other than glass vials and stoppers.

[1] FDA recognizes that during the COVID-19 public health emergency some injectable products, either approved or pending approval, may need some changes to the primary packaging components (e.g., glass vials and stoppers) due to supply chain issues affecting their availability. Although this guidance does not principally address data recommendations for original applications pending approval, the risk-based regulatory approaches discussed in this guidance, other guidance documents referenced in section VII, References, and the data recommendations provided in the tables in Appendix A may be useful during product development and for original application submission. Should an applicant need to change CCS components before product approval, the applicant should proactively seek feedback from the appropriate FDA review division to mitigate the effect of the change on the review timeline of the pending application.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020, titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," *available at* https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

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 FDA guidances means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[2] In addition, on March 13, 2020, there was a Presidential declaration of a national emergency in response to COVID-19.[3]

Many FDA-regulated human drugs (finished pharmaceuticals and biological products) related to, and products being developed for, the treatment and prevention of COVID-19 use glass vials and stoppers as their primary CCS. The supply of CCS components for FDA-regulated products generally may become constrained as manufacturers respond to the public health emergency related to COVID-19. As a result, manufacturers of FDA-regulated products may need to update their approved applications to make changes to CCS components to meet current product demand or increase supply resilience. In response to this public health emergency, FDA will

[2] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[3] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), *available at* https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

consider risk-based approaches to facilitate implementation of chemistry, manufacturing, and controls (CMC) changes to a CCS in an effort to mitigate the disruptive effect of the COVID-19 pandemic. These measures may include, but may not be limited to, recommendations for adjustments to submission content and reduction in reporting categories for CMC changes.

III. Regulatory Approach to CMC Changes

As described in 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12, an applicant must notify FDA about changes in each condition (e.g., the product, production process, quality controls, equipment, facilities, or labeling) established in an approved application beyond the variations already provided for in the application. The reporting category for such changes depends on the potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Therefore, changes can range from those that require approval before implementation (prior approval supplement (PAS)), those that require notification 30 days before (changes being effected in 30 days (CBE-30)), or upon implementation (changes being effected), and those where notification can be provided after implementation (annual report). Some of these identified changes, depending on the circumstances, may be more appropriately submitted as an original application instead of as supplements.[4]

FDA has conveyed additional clarification regarding reporting of CMC changes to an NDA, BLA, and ANDA in guidance documents specific to various application types and product dosage forms (see section VII., References). The content in section IV., Common Changes Related to Glass Vials and Stoppers, related to changes to glass vials and stoppers for finished drug and biological products includes content derived from the referenced guidance documents.

FDA applies a risk-based approach to the evaluation of proposed CMC changes to a CCS (e.g., changes in components, composition, container type, suppliers and manufacturers), taking into consideration the characteristics of the specific product. The suitability and compatibility of a CCS depends not only on the properties of a container, but also on the properties of other CCS components and their interactions with the drug product formulation over its intended shelf life. Applicants must validate the effects of the change prior to distribution of the drug,[5] and, as appropriate, conduct additional qualification tests or submit information to address product-specific risks as part of that assessment. For example, this additional information to be submitted to FDA could include studies to assess: the effect of formulation attributes such as high pH; the effect of factors that increase the potential for glass delamination, particulate matter, leachables, or interactions of labile molecules with leachables (such as susceptibility of some proteins to interact with metal ions); or the effect of the lyophilization process on product quality. Finally,

[4] Applicants can consult the appropriate Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research review division for questions regarding circumstances where an original application or supplement should be submitted.

[5] See section 506A(b) of the FD&C Act and pertinent regulations at 21 CFR 314.70(a)(2), 21 CFR 314.97(a) (incorporating 21 CFR 314.70 by reference), and 21 CFR 601.12(a)(2).

applicable tests and studies as outlined in United States Pharmacopeia (USP) chapters[6] should be conducted to demonstrate the suitability of the glass vial following a change; such tests must be conducted where needed to ensure continued compliance with compendial standards for strength, quality, or purity of the drug.[7] FDA encourages applicants to submit the appropriate postapproval supplement type as recommended by the existing guidance documents for proposed changes to the CCS.

As discussed in section V., Tools to Facilitate Changes to CCS Components, of this guidance and the guidance for industry *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency; Questions and Answers* (August 2020),[8] FDA may consider available risk evaluations and product quality risk mitigation strategies to support a lower reporting category for specific changes. FDA recommends applicants use the risk management principles described in the ICH guidance for industry *Q9 Quality Risk Management* (June 2006) where appropriate. Whether or not a change is required to be reported to FDA, in accordance with applicable regulations,[9] FDA expects all changes to be appropriately managed by an establishment's/facility's pharmaceutical quality system under the applicable current good manufacturing practice regulations in 21 CFR parts 210, 211, and 600. Applicants should also refer to the recommendations in the ICH guidance for industry *Q10 Pharmaceutical Quality System* (April 2009).

The supplement for a CCS-related change should include information to support the proposed change and can incorporate certain information by reference to a drug master file (DMF), where appropriate. However, when incorporating information by reference to a DMF, the supplement should also include sufficient product-specific information to support the change.

Applicants are ultimately responsible for assessing the effects of the proposed change(s) on product quality, and ensuring that information to support the change is provided for a complete submission of a supplement or annual report.[10] DMF holders must notify affected authorized parties of any DMF changes, additions, or deletions.[11] DMF holders also should provide application holders with sufficient information to determine the appropriate reporting procedure for their applications based on the potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. This notification should occur well before making any changes to permit authorized parties to submit application changes within an appropriate time frame. For additional information on DMF submission guidelines, refer to 21 CFR 314.420, 21 CFR 601.51(a), and the draft guidance for industry *Drug Master Files* (October 2019).[12]

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[6] See USP General Chapters <381> Elastomeric Closure for Injections, <660> Glass Containers Used in Pharmaceutical Packaging/Delivery Systems, <1207> Package Integrity Evaluation — Sterile Products, <1660> Evaluation of the Inner Surface Durability of Glass Containers.

[7] See section 501(b) of the FD&C Act.

[8] 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.

[9] 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12

[10] 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12

[11] 21 CFR 314.420(c)

[12] In June 2014, FDA issued the guidance for industry *Drug Master Files: Guidelines*. In October 2019, FDA issued the revised draft guidance for industry *Drug Master Files*. When final, this guidance will represent FDA's current thinking on this topic.

This guidance is not intended to alter existing submission processes; applicants should follow the recommendations in current guidance documents for reporting CMC changes to an approved application (see section VII., References).

IV. Common Changes Related to Glass Vials and Stoppers

The tables in Appendix A of this guidance include information derived from existing FDA guidance documents that contain recommendations for reporting category and submission content related to common CMC changes to CCS components (glass vials and stoppers) for finished drug and biological products. The tables include the type of data recommended to support a specific change (as discussed in the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation* (May 1999)), as well as the recommended reporting category. Some submission data recommendations and reporting categories may differ based on the nature of the product and the potential risk to product quality, as it may relate to safety and effectiveness of the product. The quantity of data that should be included in the submission depends on the application type and available body of knowledge.[13] Changes should be supported with confirmatory[14] batch data. To assess the change, FDA may request that the applicant provide additional information in the supplement or referenced DMF.

An applicant seeking to make more than one related change concurrently should submit a supplement with data appropriate to address the potential risk from the cumulative effect of multiple changes. Where the recommended reporting categories for the individual changes differ, the submission category selected should be the one associated with the highest risk change (e.g., PAS) of the categories recommended for the individual changes.

When the CCS changes described in the tables in Appendix A necessitate a corresponding change in finished product specifications,[15] the applicant should provide all studies and data appropriate to support the affected specification change(s). The reporting category depends on the potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. For example,

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[13] The quantity of data recommended in the tables in Appendix A for NDAs, ANDAs, and BLAs is derived from related guidance documents. For example, the number of batches is derived from principles outlined in scale-up and postapproval changes guidance documents (e.g., 1 to 3 batches for ANDAs and NDAs depending on the body of knowledge). Where guidance documents do not provide specific information on the quantity of data expected to support the change, the applicant may contact FDA to obtain feedback.

[14] For the purposes of this guidance, *confirmatory data* means comparative product batch data (on product manufactured prior to and after the proposed change) that is sufficient to demonstrate no adverse effect on product quality due to the proposed CCS change.

[15] The ICH guidances for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000) and *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999) define *specifications* as "a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described."

tightening the acceptance criteria for a quality attribute may warrant a lower reporting category than widening the acceptance criteria.

Before introducing a new CCS component that differs from the specified CCS component type/grade in product labeling (e.g., "packaged in type 1 glass"), a supplement to change product labeling may be appropriate. When the CCS new component differs from that specified in the applicable USP monograph, appropriate engagement with USP regarding an update to the product monograph[16] may be necessary.

V. Tools to Facilitate Changes to CCS Components

For CCS and component changes that are the subject of this guidance, FDA intends to consider risk-based approaches under existing tools and capabilities to facilitate providing timely feedback, guidance, and assessment[17] of proposed changes as discussed below.

FDA may expedite the assessment of a supplement or determine that a different reporting category is appropriate, taking into account public health priorities[18] and the applicant's rationale and associated risk assessment and mitigation strategy for the proposed change. Should a different reporting category be determined to be appropriate, FDA will notify the applicant and convey its rationale for the determination.

A. Risk-Based Considerations for Supplement Reporting Categories

During this public health emergency, FDA will consider requests to submit certain changes to CCS using a lower reporting category than that recommended in existing guidance if the applicants are experiencing constrained supply of CCS or components thereof, and if the relevant NDAs, ANDAs, or BLAs are related to the treatment or prevention of COVID-19 or other drugs in shortage, as appropriate. Consistent with applicable regulations and existing guidance documents related to postapproval CMC changes for drug applications and BLAs, FDA may consider available information and approaches to mitigate the risk to product quality when determining whether a lower reporting category for supplements is appropriate. Applicants

[16] For additional information, see the draft guidance for industry *Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process* (July 2019). When final, this guidance will represent FDA's current thinking on this topic.

[17] For FDA policies describing expedited review requests related to prior approval supplements to NDAs and BLAs, see MAPP 5310.3 Rev 1 *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes*; 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*; for FDA policies on drug shortage management, see MAPP 4190.1 Rev. 3 *Drug Shortage Management.* MAPPs are available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

[18] For additional information, see 21 CFR 314.70(b)(4) and MAPP 5310.3 Rev. 1 *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes.*

wishing to request a lower supplement reporting category should provide (1) their rationale, (2) supporting information, and (3) risk-mitigation approaches, for FDA to consider whether the requested reduction in reporting category is appropriate.

Before submitting a supplement with a lower reporting category than what is required in existing regulations and recommended in existing guidance, applicants should contact FDA for feedback and concurrence. For Center for Drug Evaluation and Research (CDER)-regulated products, applicants should send an email to CDER-OPQ-Inquiries@fda.hhs.gov should circumstances resulting from the COVID-19 pandemic warrant the use of atypical or flexible submission strategies as described in this section.[19] For Center for Biologics Evaluation and Research (CBER)-regulated products, applicants should contact the appropriate CBER review office. Additionally, if the CDER- or CBER-regulated product could enter, or is currently in, drug shortage, then the respective applicant should include CDER DRUG SHORTAGES (DRUGSHORTAGES@FDA.HHS.GOV) for products regulated by CDER and cbershortage@fda.hhs.gov for products regulated by CBER on those communications.

For more information, refer to the guidance for industry *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency; Questions and Answers*.

B. Comparability Protocols

As explained in the draft guidance for industry *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016),[20] a comparability protocol (CP) is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC postapproval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product. It is a tool for applicants to obtain feedback from FDA on prospective scientific approaches, submitted as a 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, supporting information (including any analysis and risk assessment activities), the plan for implementing the change(s), and, if appropriate, the proposed reduced reporting category for the change(s). By delineating the specific approach to be used to evaluate one or more future changes and the rationale for that approach, the applicant can gain the Agency's approval of the plan well in advance of the need to implement the change(s). This process can facilitate a more efficient submission process for the applicant and review process for FDA.

If the original application or PAS containing the CP is approved, the change usually can be implemented under a lower reporting category than would normally be expected based on recommendations in guidance (e.g., changes otherwise requiring a prior approval supplement could be implemented under a CBE-30). A CP can then be used for a one-time change(s) or be

[19] Regarding a pending supplement for a CDER-regulated product, applicants should contact the regulatory project management staff (regulatory project manager or regulatory business process manager) within the appropriate CDER review office responsible for the subject product application.

[20] See this guidance for additional information. When final, this guidance will represent FDA's current thinking on this topic.

used repeatedly for a specified type of change over the life cycle of a product. A CP can also be submitted to cover an identical change(s) that affects multiple applications (grouped supplements, trans-BLA submissions).[21] A CP is a well-suited tool for making changes to glass vials and stoppers, because a change to one component can be implemented to many products sharing that container or closure, and the protocol could be used multiple times as the need arises for additional changes to accommodate the dynamic supply chain evolution in reaction to COVID-19.

VI. Additional Resources

For additional questions about this guidance, contact CDER at CDER-OPQ-Inquiries@fda.hhs.gov, or contact the CBER office responsible for the product's regulation. The text "COVID-19 Container Closure System and Component Changes" should be included in the subject line of the email.

Depending on regulatory jurisdiction of the product application, the applicant can contact the responsible review division within CDER or CBER (as applicable) to gain additional feedback on specific changes, the information needed to support the change, and the filing approach, as needed.

VII. References[22,23,24]

Draft and Final Guidances

- *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)
- *Changes to an Approved NDA or ANDA* (April 2004)
- *Changes to an Approved NDA or ANDA; Questions and Answers* (January 2001)

[21] See the draft guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[22] 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.

[23] MAPPs can be found on the CDER Manual of Policies & Procedures web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp, and SOPPs can be found on the Biologics Procedures (SOPPs) web page at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-procedures-sopps.

[24] For a comprehensive list of COVID-19 guidance documents, see the COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders web page at (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders).

- *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)[25]

- *Container Closure Systems for Packaging Human Drugs and Biologics; Chemistry, Manufacturing, and Controls Documentation* (May 1999)

- *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014)

- *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)[26]

- *Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information* (April 2016)[27]

- *Drug Master Files* (October 2019)[28]

- *Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process* (July 2019)[29]

- *Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency; Questions and Answers* (August 2020)

- *PAC-ATLS: Postapproval Changes — Analytical Testing Laboratory Sites* (April 1998)

- *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)

Scale-Up and Postapproval Changes Guidances

- *Immediate Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)

- *Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)

- *SUPAC: Manufacturing Equipment Addendum* (December 2014)

[25] When final, this guidance will represent the FDA's current thinking on this topic.
[26] Ibid.
[27] Ibid.
[28] In June 2014, FDA issued the guidance for industry *Drug Master Files: Guidelines*. In October 2019, FDA issued the revised draft guidance for industry *Drug Master Files*. When final, this guidance will represent FDA's current thinking on this topic.
[29] When final, this guidance will represent the FDA's current thinking on this topic.

- *SUPAC-IR: Questions and Answers about SUPAC-IR Guidance* (February 1997)

- *SUPAC-MR: Modified Release Solid Oral Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (September 1997)

ICH Guidances

- *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)

- *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999)

- *Q9 Quality Risk Management* (June 2006)

- *Q10 Pharmaceutical Quality System* (April 2009)

Manual of Policies and Procedures

- MAPP 4190.1 Rev. 3 *Drug Shortage Management*

- MAPP 5240.3 Rev. 5 *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*

- MAPP 5310.3 Rev. 1 *Requests for Expedited Review of New Drug Application and Biologics License Application Prior Approval Supplements Submitted for Chemistry, Manufacturing, and Controls Changes*

Standard Operating Procedures and Policies

- SOPP 8506 *Management of Shortages of CBER-Regulated Products*

Appendix A: Tables Describing CCS Changes for Products With Approved ANDAs, NDAs, or BLAs

The following tables include information derived from existing FDA guidance documents containing FDA recommendations for reporting categories and submission content for common chemistry, manufacturing, and controls changes to glass vials and stoppers, the container closure system (CCS) components of finished pharmaceuticals and biological products. These tables provide baseline recommendations for the information to be submitted and the reporting category for specific changes, and do not consider the cumulative effect of concurrent changes. As stated in sections IV and V of the guidance, FDA may request more information to support the change, and determine that a different reporting category is appropriate based on risk assessment information related to the specific change proposed.

These tables do not include all possible CCS changes that would necessitate a submission as described in applicable regulations.[1] Application holders should consult existing guidance documents for further information on CCS change recommendations. Depending on regulatory jurisdiction of the product application, the applicant can contact the responsible review division within the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) (as applicable) to gain additional feedback on specific changes, the information needed to support the change, and the filing approach, as needed.

For the following tables, the term *confirmatory data* means comparative data that demonstrate no adverse impact on product quality due to the proposed CCS change.

[1] 21 CFR 314.70, 21 CFR 314.97, and 21 CFR 601.12

Table A: Changes to the Properties of Glass Vials and Stoppers: New Drug Applications/Abbreviated New Drug Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change from glass to a new material (e.g., plastic)	Confirmatory batch data, including release and stability data (accelerated and real time▪), and data to support sterility assurance Extractables and leachables risk assessment and supporting data	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA* (April 2004)	
Change to different composition or type of glass[2]	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	Sections IX.B.4. and IX.C.1.a. of *Changes to an Approved NDA or ANDA*	FDA may consider a lower reporting category based on the circumstances of the specific change[2]

continued

Table A, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change between molded and tubing glass	Description, composition, drawing, and specification of vial CCS suitability tests and determinations as recommended in USP General Chapter <660> and principles of USP General Chapter <1660> (required for compendial products)[3] Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance CCIT data Lyophilization cycle verification or validation if process is modified (refer to Specific Considerations for Reporting Category)	CBE-30 PAS for lyophilized products (refer to Specific Considerations for Reporting Category)	Section IX.C.1.a. of *Changes to an Approved NDA or ANDA*	Changes in vial properties that affect manufacturing processes (e.g., thicker glass affecting lyophilization processes) pose a higher risk to quality and therefore may trigger a higher reporting category with additional data needed to assess the effects of the change

continued

Table A, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change in vial dimensions	CCIT data Representative media fill/bracketing data Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA*	For vials with the same nominal fill volume but slight changes to dimensions, a CBE-30 may be appropriate
Switch from amber glass to clear glass (with or without additional photoprotective measures)	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance Additional tests based on results of comparative photostability study Labeling change accounting for different storage conditions (e.g., protect from light)	PAS	Section IX.B.6. of *Changes to an Approved NDA or ANDA*	

continued

Table A, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change in primary CCS type (e.g., switching from vial to ampule)[4]	Description of the container properties and composition Container suitability[5] Manufacturing and controls CCIT data Sterilization validation Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA*	

continued

Table A, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change in stopper rubber/elastomer material[6]	Description of new stopper Composition Manufacturing and controls Closure suitability[7] CCIT data Confirmatory batch data, including release and stability data (accelerated and real time), including vial orientations where formulation is in contact with stopper, and data to support sterility assurance	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA*	
Change in stopper dimensions	CCIT data Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	CBE-30	Section IX.C.1.a. of *Changes to an Approved NDA or ANDA*	

continued

Table A, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Changes in how the stopper is supplied (e.g., unprocessed, RTS, and RTU)	Sterilization and depyrogenation validation Representative COA, which would include sterility and BET data if stoppers are supplied RTU and BET data if stoppers are supplied RTS	CBE-30	Section IX.C.1.a. of Changes to an Approved NDA or ANDA	

* PAS = prior approval supplement; CCIT = Container Closure Integrity Test; CBE-30 = changes being effected in 30 days; RTS = ready to sterilize; RTU = ready to use; COA = certificate of analysis; BET = bacterial endotoxins testing

▪ *Accelerated and real time* refers to batch stability data from accelerated and long-term studies, respectively.

[1] 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.

[2] A change in glass supplier without a change in glass type or coating and without a change in container/closure dimensions can be filed as an annual report as described in section 5.4 of Appendix A in the guidance for industry *CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports* (March 2014).

[3] United States Pharmacopeia (USP) General Chapter <660> Glass Containers Used in Pharmaceutical Packaging/Delivery Systems, and USP General Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers

[4] Some of these identified changes, depending on the circumstances, may be more appropriately submitted as an original application instead of as supplements. This type of change may also warrant a labeling change supplement to account for a new presentation. Application holders should follow existing FDA guidance. Applicants can consult the appropriate review division within CDER or CBER if there are questions.

[5] Information about the suitability of proposed glass with respect to protection (e.g., container integrity for sterility), safety (e.g., extractables and leachables) and performance. Application holders should refer to USP General Chapter <660> and USP General Chapter <1660> for further information.

[6] When alternate suppliers of stoppers are proposed, and if there are differences in stopper properties or manufacturing processes changes between the currently approved and proposed supplier, because of the increased risk to quality, a higher reporting category — PAS — is warranted. However, if the differences in stopper properties and manufacturing processes are minimal then a lower reporting category may be considered.

[7] Information about the suitability of proposed stopper with respect to protection (e.g., container integrity for sterility), safety (e.g., extractables and leachables) and performance. Application holders should refer to USP General Chapter <381> Elastomeric Closure for Injections, for additional information.

Table B: Changes to the Properties for Glass Vials and Stoppers: Biologics License Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change from glass to a new material (e.g., plastic)	Extractables and leachables risk assessment and supporting data Confirmatory batch data, including release and stability data (accelerated and real time▪), and data to support sterility assurance	PAS	*Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997) Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)[2]	

continued

Table B, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change to different composition or type of glass[3]	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	BLA: *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products*	FDA may consider a lower reporting category based on the circumstances of the specific change (e.g., if the new vial type or composition was previously used in a licensed product)

continued

Table B, continued

Proposed Change	**Recommended Information to Support the Change**	**Recommended Reporting Category**	**Reference to Current Guidance[1]**	**Specific Considerations for Reporting Category**
Change between molded and tubing glass	Description, composition, drawing, and specification of vial CCS suitability tests and determinations as recommended in USP General Chapter <660> and principles of USP General Chapter <1660> (required for compendial products)[4] CCIT data Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance Lyophilization cycle verification or validation if process is modified (refer to Specific Considerations for Reporting Category)	AR PAS for lyophilized products with molded vials (refer to Specific Considerations for Reporting Category)	Section 3.2.P.7., due to expected change in properties, of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* Section 5.2 of the Appendix in CMC *Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)[5] *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	Changes in vial properties that affect manufacturing processes (e.g., thicker glass affecting lyophilization processes) pose a higher risk to quality and therefore may trigger a higher reporting category with need for additional data to assess the effects of the change

continued

Table B, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change in vial dimensions	CCIT data Representative media fill Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance Additional accelerated and real time stability data as needed (e.g., concurrent stopper change)	PAS	BLA: *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products*	For vials with the same nominal fill volume but slight changes to dimensions, a CBE-30 may be considered
Switch from amber glass to clear glass (with or without additional photoprotective measures)	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance Additional tests based on results of comparative photostability study Labeling change accounting for different storage conditions (e.g., protect from light)	PAS	Same as above	

continued

Table B, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change in primary CCS type (e.g., switching from vial to ampule)[6]	Description of the container properties and composition Container suitability[7] Manufacturing and controls Sterilization validation CCIT data Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	BLA: *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products*	

continued

Table B, continued

Proposed Change	**Recommended Information to Support the Change**	**Recommended Reporting Category**	**Reference to Current Guidance[1]**	**Specific Considerations for Reporting Category**
Change in stopper rubber/elastomer material[8]	Description of new stopper Composition Closure suitability[9] Manufacturing and controls CCIT data Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	BLA: *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products*	
Change in stopper dimensions	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance CCIT data	CBE-30	Same as above	

continued

Table B, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Changes in how the stopper is supplied (e.g., unprocessed, RTS, and RTU)	Sterilization and depyrogenation validation Confirmatory batch data, including data to support sterility assurance	CBE-30	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., change is occurring at a vendor that provides pre-processed stoppers)

* PAS = prior approval supplement; BLA = biologics license application; CCIT = Container Closure Integrity Test; AR = annual report; CBE-30 = changes being effected in 30 days; RTS = ready to sterilize; RTU = ready to use

▪ *Accelerated and real time* refers to batch stability data from accelerated and long-term studies, respectively.

[1] 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.

[2] When final, this guidance will represent the FDA's current thinking on this topic.

[3] This change can be reported in an annual report if there is no change in the product-contact material or dimensions (size and shape) per 3.2.P.7 of the Appendix in the draft guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products.*

[4] United States Pharmacopeia (USP) General Chapter <660> Glass Containers Used in Pharmaceutical Packaging/Delivery Systems, and USP General Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] Some of these identified changes, depending on the circumstances, may be more appropriately submitted as an original application instead of as supplements. This type of change may also warrant a labeling change supplement to account for a new presentation. Application holders should follow existing FDA guidance. Applicants can consult the appropriate review division within CDER or CBER if there are questions.

[7] Information about the suitability of proposed glass with respect to protection (e.g., container integrity for sterility), safety (e.g., extractables and leachables) and performance. Application holders should refer to USP General Chapter <660> and USP General Chapter <1660> for further information.

[8] When alternate suppliers of stoppers are proposed, and if there are differences in stopper properties or manufacturing processes changes between the currently approved and proposed supplier, because of the increased risk to quality, a higher reporting category — PAS — is warranted. However, if the differences in stopper properties and manufacturing processes are minimal then a lower reporting category may be considered.

[9] Information about the suitability of proposed stopper with respect to protection (e.g., container integrity for sterility), safety (e.g., extractables and leachables) and performance. Application holders should refer to USP General Chapter <381> Elastomeric Closure for Injections, for additional information.

Table C: Changes to the Source or Site of Manufacture for Glass Vials and Stoppers: New Drug Applications/Abbreviated New Drug Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Site of vial or stopper manufacture or processing (no change in supplier)	Name and address of the new site Comparative information on the CCS between the old and the new source Commitment to place batches on stability	AR	Section VI.A. of *Changes to an Approved NDA or ANDA* (April 2004)	
Site of vial or stopper sterilization	Name and address of the new site Validation data to support the vial/stopper sterilization	AR (when the process is not materially different from that provided for in the approved application)	Section VI.D.4. of *Changes to an Approved NDA or ANDA*	
Site of vial or stopper testing	Name and address of the new site Full description of the testing to be performed by the new facility	CBE-30	Section VI.C.1.d. of *Changes to an Approved NDA or ANDA* *PAC-ATLS: Postapproval Changes — Analytical Testing Laboratory Sites* (April 1998)	

* AR = annual report; CBE-30 = changes being effected in 30 days

[1] 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.

Table D: Changes to the Source or Site of Manufacture for Glass Vials and Stoppers: Biologics License Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Site of vial or stopper manufacture or processing (no change in supplier)	Name and address of the new site Comparative information on the CCS between the old and the new source Commitment to place batches on stability	AR	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)[2] *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)	For certain biological products, a higher reporting category may be appropriate if vial or stopper manufacturing or processing will be done by the drug product manufacturer

continued

Table D, continued

Proposed Change	**Recommended Information to Support the Change**	**Recommended Reporting Category**	**Reference to Current Guidance[1]**	**Specific Considerations for Reporting Category**
Site of vial or stopper sterilization	Name and address of the new site Validation data to support the vial/stopper sterilization	CBE-30	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* Section 5.2 of the Appendix in *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)[3] *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vendor provides pre-sterilized stoppers and is changing site of sterilization).
Site of vial or stopper testing	Name and address of the new site Full description of the testing to be performed by the new facility	AR	*CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports*	

* AR = annual report; CBE-30 = changes being effected in 30 days

[1] 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

[2] When final, this guidance will represent the FDA's current thinking on this topic.

[3] Ibid.

Table E: Changes to the Manufacturing or Processing of Glass Vials and Stoppers: New Drug Applications/Abbreviated New Drug Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Changes in vial sterilization or depyrogenation method (e.g., changing from moist to dry heat)	Validation data to support the sterilization or depyrogenation method change Extractables and leachables data Accelerated and real time▪ stability data	PAS	Section VII.B.2. of *Changes to an Approved NDA or ANDA* (April 2004)	
Changes in vial sterilization or depyrogenation process parameters	Validation data to support the sterilization/depyrogenation process change	CBE-30	Section VII.C.1.d. of *Changes to an Approved NDA or ANDA*	
Stopper washing process	Validation data to support the depyrogenation process change	CBE-30	Section VII.C.1.a. of *Changes to an Approved NDA or ANDA*	
Stopper siliconization process	CCIT data if a new coating is used Extractables and leachables data Accelerated and real time stability data	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA*	

continued

Table E, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Changing the method of stopper sterilization (e.g., from moist heat to irradiation)	Validation data to support the sterilization/depyrogenation process change Extractables and leachables data Accelerated and real time stability data	PAS	Section VII.B.2. of *Changes to an Approved NDA or ANDA*	
Stopper sterilization process parameters	Validation data to support the sterilization/depyrogenation process change	CBE-30	Section VII.C.1.a. of *Changes to an Approved NDA or ANDA*	

* PAS = prior approval supplement; CBE-30 = changes being effected in 30 days; CCIT = Container Closure Integrity Test

▪ *Accelerated and real time* refers to batch stability data from accelerated and long-term studies, respectively.

[1] 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.

Table F: Changes to the Manufacturing or Processing of Glass Vials and Stoppers: Biologics License Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Changes in vial sterilization or depyrogenation method (e.g., changing from moist to dry heat)	Validation data to support the sterilization or depyrogenation method change Extractables and leachables data Accelerated and real time▪ stability data	PAS	*Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)[2]	
Changes in vial sterilization or depyrogenation process parameters	Validation data to support the sterilization or depyrogenation process change	CBE-30	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017)[3] *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vial vendor is changing the sterilization or depyrogenation process parameters)

continued

Table F, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Stopper washing process	Depyrogenation validation data to support the stopper washing process change	CBE-30	Section 5.2 of the Appendix in *CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports* (August 2017)[4] Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vendor provides pre-washed stoppers and is changing the washing process)

continued

Table F, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Stopper siliconization process	CCIT data if a new coating is used Extractables and leachables data Accelerated and real time stability data	CBE-30	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vendor provides pre-siliconized stoppers and is changing the siliconization process)
Changing the method of stopper sterilization (e.g., from moist heat to irradiation)	Validation data to support the stopper sterilization method change Extractables and leachables data Accelerated and real time stability data	PAS	*Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*[5]	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vendor is changing the sterilization method)

continued

Table F, continued

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Stopper sterilization process parameters	Validation data to support the stopper sterilization process change	CBE-30	Section 3.2.P.7. of the Appendix in *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*	For certain biological products, FDA may consider AR depending on the circumstances of the change (e.g., vendor provides pre-sterilized stoppers and is changing the sterilization process)

* PAS = prior approval supplement; CBE-30 = changes being effected in 30 days; AR = annual report; CCIT = Container Closure Integrity Test

▪ *Accelerated and real time* refers to batch stability data from accelerated and long-term studies, respectively.

[1] 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.

[2] See also 21 CFR 601.12(b)(2)(vi).

[3] When final, this guidance will represent the FDA's current thinking on this topic.

[4] Ibid.

[5] See also 21 CFR 601.12(b)(2)(vi).