# Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA

## 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)**

**October 2022**
**Pharmaceutical Quality/CMC**

# Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA

## Guidance for Industry

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

**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)**

**October 2022**
**Pharmaceutical Quality/CMC**

## TABLE OF CONTENTS

*Contains Nonbinding Recommendations*

# Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA
# Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. With the exception of the discussion in section V regarding submission of certain modifications to an approved comparability protocol in a changes being effected supplement or annual report,[2] 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 final guidance is intended to assist original applicants and holders of approved new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) with implementing a chemistry, manufacturing, and controls (CMC) postapproval change through the use of a *comparability protocol* (CP).[3] A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed postapproval CMC change(s) on the identity, strength, quality, purity, and potency of a drug product, including a biological product (i.e., *product*),[4] as these factors may relate to the safety or effectiveness of the product (i.e., *product quality*).[5,6]

Submission of a CP in an original application or in a prior approval supplement (PAS) to an approved application allows FDA to review a description of one or more proposed CMC

[1] This guidance has been prepared by the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration (FDA).

[2] This limited portion of the guidance has a binding effect on the FDA and holders of approved NDAs, ANDAs, and BLAs, pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as implemented in 21 CFR 314.70 for NDAs and 601.12 for BLAs. For ANDAs, 21 CFR 314.70 is referenced in 314.97.

[3] "Comparability protocol" in this guidance is synonymous with "postapproval change management protocol (PACMP)" in the International Council for Harmonisation (ICH) guidance for industry *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management and its Annexes* (May 2021) (ICH Q12).

[4] For the purposes of this guidance, unless otherwise specified, references to "drugs" "drug products", and "products" include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262). Also, see definitions of "drug product" and "biological product" in 21 CFR 314.3 and 600.3, respectively.

[5] In this guidance, "product quality" refers to the identity, strength, quality, purity, and potency of a product, as these factors may relate to the safety or effectiveness of the product.

[6] See also section 506A(b) of the FD&C Act (21 U.S.C. 356a(b)) and the definitions for "assess the effects of the change" in 21 CFR 314.3 and 600.3.

postapproval changes, any supporting information and analysis, including a risk assessment, a plan to implement the change(s), and, if appropriate, a proposed reduced reporting category for the change(s). Approval of the original application or a subsequent PAS containing the CP provides an agreed-upon plan to implement the specified change(s), and in many cases, a justification to report the change(s) in a reduced reporting category, contingent upon your analysis of the data from the implementation of the change(s). In many cases, submission and approval of a CP will facilitate the subsequent implementation and reporting of CMC changes, which could result in moving a product into distribution or facilitating a proactive approach to reinforcing the supply of the product sooner than if a CP were not used. The drivers for such changes include business needs, expanding markets, process improvements, potential for drug shortage, and accelerated manufacturing development that sometimes occurs with drugs eligible for expedited programs.[7]

This guidance recommends a framework to promote innovation and continuous improvement in the manufacturing of quality products by encouraging you to employ:

- Effective use of knowledge and understanding of the product and manufacturing process
- Risk management activities over the life cycle of a product
- An effective pharmaceutical quality system

This guidance applies to CPs submitted in NDAs, ANDAs, BLAs, and supplements to these applications regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). However, this guidance is not applicable to blood and blood components; biological products that also meet the definition of a device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); or human cells, tissues, or cellular or tissue-based products (HCT/Ps) regulated solely under section 361 of the Public Health Service Act and 21 CFR part 1271. Recommendations for the use of CPs by manufacturers of licensed blood and blood components are included in a separate FDA guidance for industry on *Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture* (December 2014). The scope of this guidance does not include animal drugs.

This guidance incorporates the modern regulatory concepts stated in FDA's guidance for industry on *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing,*

[7] See FDA guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). We update 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 page at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

*and Quality Assurance* (September 2004),[8] the Pharmaceutical Quality for the 21st Century—A Risk Based Approach,[9] the Critical Path Initiative,[10] and the quality-by-design principles described in the International Conference for Harmonisation (ICH) guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009) (ICH Q8(R2)). These principles are also incorporated in the following ICH guidances: *Q9 Quality Risk Management* (June 2006) (ICH Q9), *Q10 Pharmaceutical Quality System* (April 2009) (ICH Q10), *Q11 Development and Manufacture of Drug Substances* (November 2012) (ICH Q11), and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and its *Annexes* (May 2021) (ICH Q12).

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 as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

An exception to that framework derives from section 506A of the FD&C Act, as implemented in 21 CFR 314.70 and 601.12. Accordingly, insofar as this guidance sets forth that certain modifications to an approved CP must be submitted in a changes being effected supplement or annual report for a less burdensome reporting category than a PAS, portions of this document are not subject to the usual restriction in the above paragraph or in FDA's good guidance practice regulations that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d). Therefore, to the extent that section V of this guidance sets forth that certain modifications to an approved CP must be submitted in a changes being effected supplement or annual report rather than a PAS, it has a binding effect, as indicated by the use of the words *must*, *shall*, or *required*.[11]

## II. BACKGROUND

You are responsible for validating the effects of any postapproval manufacturing change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug before distribution of the drug made with the change.[12] You must notify FDA of a change to the conditions established in an approved application in accordance with the regulatory requirements outlined in 21 CFR 314.70 or 601.12. In those regulations,

---

[8] This guidance is intended to provide recommendations for flexible approaches to implementation of advanced control approaches. In addition to the PAT guidance cited above, information about implementing PAT can be found in *Questions and Answers on Current Good Manufacturing Practices – Production and Process Controls* (September 2013).

[9] See https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/pharmaceutical-quality-21st-century-risk-based-approach-progress-report.

[10] See http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm.

[11] See footnote 2.

[12] See section 506A of the FD&C Act (21 USC 356a), 21 CFR 314.70, and 601.12. A holder of an approved application under section 505 of the FD&C Act (21 USC 355) must assess the effects of the change before distributing a drug product made with a manufacturing change (see 21 CFR 314.70(a)(2)). For biological products, an applicant is required to demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product (see 21 CFR 601.12(a)(2)).

postapproval CMC changes to the conditions established in approved applications are categorized into one of three reporting categories depending on whether the change(s) has a substantial, moderate, or minimal 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.[13] If a change has a substantial 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 (a major change), you must submit and receive FDA approval of a PAS before the product made with the manufacturing change is distributed in accordance with 21 CFR 314.70(b) or 601.12(b). If a change has a moderate 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 (a moderate change), you must submit a supplement at least 30 days before the product is distributed (a changes being effected in 30 days (CBE-30) supplement) or, in some cases, begin distribution upon receipt by FDA of a supplement for the change (CBE-0 supplement) in accordance with 21 CFR 314.70(c) or 601.12(c). If a change has a minimal 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 (a minor change), you may proceed with the change, but must notify FDA of the change in the next annual report in accordance with 21 CFR 314.81 and 314.70(d) or 601.12(d), as applicable.

The regulations also provide for comparability protocols as an option for managing postapproval manufacturing changes in accordance with 21 CFR 314.70(e) or 601.12(e).[14] Such protocols can be submitted in an original application or can be submitted in a PAS.[15]

Regardless of the type of change, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of a product, including packaging and labeling operations, testing, and quality control of products, must comply with current good manufacturing practice (CGMP).[16] CGMP provides for the implementation of oversight and controls over the manufacture of products to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished products. All manufacturing changes must be reviewed and approved by the quality control unit.[17] Written records required as per CGMP regulations must be maintained so that the data therein can be used for evaluating, at least annually, the quality standards of each product to determine the need for changes in product specifications or manufacturing or control procedures.[18] Other FDA and ICH guidances also discuss assessing and reporting of CMC

[13] See 21 CFR 314.70 and 601.12.
[14] Note that *manufacture* includes testing and other quality control procedures (see 21 CFR 207.1, 210.3, and 600.3).
[15] See 21 CFR 314.70(e) and 601.12(e); see also ICH Q12.
[16] See sections 501 and 704 of the FD&C Act (21 U.S.C. 351 and 21 U.S.C. 374), and 21 CFR parts 210, 211, 212, and 600-680. The CGMP regulations for finished pharmaceuticals, at 21 CFR parts 210 and 211, and the biological product regulations at 21 CFR parts 600-680 set the regulatory standard for manufacturing and quality control (note that 21 CFR parts 210 and 211 also apply to licensed biological products that are regulated as drugs under the FD&C Act). Additionally, 21 CFR part 212 sets forth CGMP regulations governing positron emission tomography drugs.
[17] See 21 CFR 211.100(a) and 211.160(a).
[18] See 21 CFR 211.180(e). For recommendations on active pharmaceutical ingredient CGMP, see ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016) (ICH Q7). For recommendations regarding an effective quality management system see ICH Q10.

postapproval changes[19] and CGMP.[20] You should refer to them in addition to this guidance when planning to make CMC postapproval changes.

## III. OVERVIEW

A CP describes the specific tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the lack of adverse effect of one or more proposed CMC changes on product quality.[21] A CP should also include the analytical procedures to be used or reference thereto.[22]

As noted above, a CP can be submitted in an original application or can be submitted in a PAS. A PAS containing the CP must be approved by FDA before the proposed changes are implemented, as outlined in the protocol, and the product is distributed in accordance with the approved reporting category (see 21 CFR 314.70(e) and 601.12(e)). A CP can be for a one-time change(s), or be 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 (e.g., grouped supplements, trans-BLA).[23]

A CP can be useful in providing predictability for the implementation of future changes to an approved product, including its manufacturing process. By delineating the specific approach to be used to evaluate one or more future changes and the rationale for that approach, you can gain FDA's approval of the plan well in advance of the need to implement the change(s). This can facilitate a more efficient process for both applicants' submissions and FDA's review. In addition, depending on the extent of available knowledge regarding the product and process, the associated risk of the proposed change(s), and the suitability of the control strategy in effect, FDA may be able to approve a protocol that justifies reporting certain changes in a manner not

---

[19] For example, see FDA guidances *Changes to an Approved NDA or ANDA* (April 2004)*; Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997)*; Immediate Release Solid Oral Dosage Forms*: *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR) (November 1995)*; Modified Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation* (SUPAC-MR) (September 1997)*; Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015); *Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (SUPAC-SS) (May 1997); *SUPAC: Manufacturing Equipment Addendum* (December 2014); *Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (April 1996); ICH guidance *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* (ICH Q5E), and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021). See also FDA draft guidance *Postapproval Changes to Drug Substances* (September 2018); when final, this guidance will represent FDA's current thinking on the topics therein.

[20] For example, see ICH Q7 and ICH Q10.

[21] See 21 CFR 314.70(e) and 601.12(e). We note that CMC changes covered by a CP may reflect appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements (see ICH Q10).

[22] Analytical procedures that you have previously submitted can be incorporated into a CP by reference to your application (see 21 CFR 314.50(g)(1)).

[23] CDER and CBER refer to an identical change(s) that affects multiple applications as grouped supplements and trans-BLA, respectively; see Appendix for further details.

requiring approval from FDA prior to distribution of a product produced with the change (i.e., a CBE-30 supplement, CBE-0 supplement, or an annual report).

FDA recommends that you consider a CP submission that proposes a reduced reporting category for particular changes only if you have a sufficient understanding of the product and manufacturing process to assess the risks associated with implementing the proposed change. Such understanding should be derived from one or more of the following, as appropriate:

- Prior knowledge (public domain or internally documented)[24]
- Development of the drug substance and its manufacturing process[25]
- Pharmaceutical development (development of the product and its manufacturing process)[26]
- Process validation activities that include process design, process qualification, and continued process verification[27]
- Quality risk management activities[28]
- Studies conducted at less than commercial scale to gain an increased understanding of the effects of the change(s) on product quality[29]

Seeking approval of a CP as part of the original application may facilitate your ability to prospectively plan to optimize the manufacturing process or otherwise adjust the control strategy rapidly and predictably in the immediate postapproval period as manufacturing experience is gained. If the product and process understanding available at the time of the original application approval is not sufficient to support the risk assessment for future changes, a CP can also be submitted in a PAS once additional commercial manufacturing experience is gained. In general, as part of its assessment of a CP and a proposed reduced reporting category, FDA intends to take into consideration the type of change and its associated potential risks, the extent of your available product and process understanding, the suitability of the control strategy, and the nature and extent of the tests and studies planned, including the acceptance criteria to be achieved, to support the change.

When you submit a CP to FDA, we recommend that the CP include a descriptive title, version number, and date for tracking purposes, and that you submit the CP in Module 3, section 3.2.R

---

[24] Prior knowledge can include established chemical, biological and engineering principles, scientific and technical literature, and applied manufacturing experience. For example, prior knowledge can include relevant knowledge and experience gained from using platform technology. Prior knowledge can be used at the beginning of development and iteratively updated with development data (including data from nonclinical and clinical studies) during the life cycle of the product. See ICH Q8(R2), ICH Q10, and ICH Q11.

[25] See, e.g., ICH Q11.

[26] See, e.g., ICH Q8(R2).

[27] See, e.g., FDA guidance for industry *Process Validation: General Principles and Practices* (January 2011).

[28] See, e.g., ICH Q9.

[29] For example, studies performed at pilot scale or laboratory scale.

Regional Information.[30] For an original application, the cover letter should note that one or more CPs has been included in the submission; for a PAS containing a CP, you should note in the cover letter that the subject of the submission is a "Comparability Protocol."

Once approved by FDA, a submission containing a CP provides an agreed-upon plan for you to perform the specified activities in the CP and implement the proposed change(s), and in many cases, a justification to report the change(s) using a reduced reporting category, contingent upon your analysis of the data from the implementation of the change(s). Notification of the change(s) using the reporting category specified in the approved CP submission is appropriate if all of the predefined acceptance criteria for success in the approved CP have been achieved. If the activities specified in the approved CP are not performed or if the predefined acceptance criteria for success are not achieved, then any reduced reporting category is not justified. In the latter case, the change(s), if pursued, must be reported in accordance with 21 CFR 314.70 or 601.12 and should follow applicable FDA guidances addressing postapproval changes.[31]

Many types of CMC changes in the drug substance, product, production process, quality controls, equipment or facilities that would ordinarily require a PAS or other postapproval supplement can be addressed in a CP submission. However, certain changes are considered not suitable for a CP because they would likely result in an unacceptably high or uncertain risk to product quality (e.g., changes that would need supportive data derived from a nonclinical safety, pharmacokinetic/pharmacodynamic, or clinical safety or efficacy study to assess the effects of the change). See the Appendix for questions and answers on using CPs for making postapproval CMC changes, including examples of changes that are considered suitable or not suitable for a CP.

## IV. COMPARABILITY PROTOCOL SUBMISSION — CONTENT RECOMMENDATIONS

The CP submission should provide a comprehensive, detailed plan for the implementation of a proposed change(s) and should include the information described below. FDA uses this information to assess whether the outcomes of any proposed test or study would or would not support the specified future change(s). Such information should be sufficient to merit the proposed reduced reporting category for the implementation of the change(s).

### A. Summary

FDA recommends that you provide a summary of the CP submission using tabular (e.g., a list of tests and studies, analytical procedures, and acceptance criteria), narrative, and/or graphic presentations, as appropriate. The summary should include a brief overview of the following:

- A description of and rationale for the proposed CMC change(s)

[30] See ICH guidance for industry *The CTD — Quality* (August 2001) (ICH M4Q).

[31] See guidances on postapproval changes listed in footnote 19. If an assessment indicates that a change has adversely affected product quality, FDA recommends that the change be submitted in a PAS regardless of the recommended reporting category for the change (see FDA guidance for industry *Changes to an Approved NDA or ANDA* (April 2004)).

- Supporting information and analysis
- Comparability protocol for the proposed change(s)
- Proposed reduced reporting category
- Other information

The remainder of the CP submission should provide the detailed information as described in sections B through F below.

### B. Description of and Rationale for the Proposed CMC Change(s)

The proposed change(s) should be described in sufficient detail to enable FDA to evaluate the relevance and adequacy of the CP. FDA recommends that you include information on the basis and rationale for the change(s), where applicable.

### C. Supporting Information and Analysis

Supporting information submitted with the CP should demonstrate your understanding of those aspects of the product, manufacturing process, risk, and control strategy that are relevant to the proposed change(s).

The supporting information should include the following, as applicable:

- Prior knowledge[32] used to justify the proposed CMC change(s)
- A summary of the risk assessment of the proposed change(s)

  The risk assessment should identify the potential effects of the change(s) on product quality.[33] The extent of the risk assessment should be commensurate with the level of risk associated with the proposed change(s). If multiple changes are proposed for simultaneous implementation or if a specified type of change will be made repeatedly over the life cycle of the product, the risk assessment should also address the potential for cumulative effects of these changes on product quality.
- Information from development of the drug substance and its manufacturing process and/or pharmaceutical development that contributes to the scientific and technological understanding of a proposed change(s) and its predicted effects on product quality.

[32] See footnote 24 regarding prior knowledge.

[33] A number of different approaches can be taken to perform risk assessments of the potential effects of the change(s) on product quality (see ICH Q8(R2), ICH Q9, and ICH Q11 for more information on possible approaches).

Development batches used to support the CP should be described according to batch size or scale, site, date of manufacture, route and/or process used, and intended purpose.

- Any studies conducted to gain an increased understanding of the proposed change(s) and the predicted effects on product quality.

  For example, studies at less than commercial scale (e.g., mechanistic evaluations, design of experiments, modeling, simulations) to identify the relationship between material attributes and process parameters to product quality attributes can be used to gain such an understanding. Also, process analytical technology (PAT)[34] can be used to enhance understanding and control of the manufacturing process.

- A discussion regarding the suitability of the control strategy, and if applicable, any changes needed to the control strategy to accommodate the planned CMC change(s).

The amount of supporting information that should be provided depends on, and is commensurate with, the complexity of the product, manufacturing process, and the planned change. For any information that is already submitted in the same NDA, ANDA, or BLA, you should simply indicate where this information can be found (e.g., provide the section number and sequence number, or volume and page number).

### D. Comparability Protocol for the Proposed CMC Change(s)

The CP for the proposed CMC change(s) should describe the specific tests and studies to be performed, including analytical procedures to be used, and acceptance criteria to be achieved to demonstrate the lack of adverse effect on product quality. The overall design of the CP should take into account your understanding of the product, manufacturing process, risks, and control strategy that are relevant to the proposed change(s). The intended use of the product should also be taken into account. The level of detail that should be provided in the CP depends on the complexity of the product, manufacturing process, and the proposed change(s), as well as the specific risks to product quality associated with the proposed change(s).

For a proposed product and/or manufacturing process change(s), the CP should typically include a comparative assessment of relevant product quality attributes before and after the change(s). A side-by-side comparison should be performed, if possible. A CP developed without such a side-by-side comparison should include appropriate justification.[35] A CP should identify the material(s) that may be affected by the proposed CMC change(s) (e.g., in-process material, drug

[34] See FDA guidance for industry *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (September 2004).

[35] For example, in cases where the pre-change material is not available, it might be possible to design a CP to compare the post-change product to established quality reference standards and/or comparator products. For complex products that are difficult to characterize (e.g., certain biological products), we recommend that you contact the appropriate FDA review division prior to submitting a CP. For questions about submitting a CP to an NDA, ANDA, or BLA in CDER, contact the Regulatory Business Process Manager in OPQ for the specific product. For questions about submitting a CP to a BLA, NDA, or ANDA in CBER, contact the Regulatory Project Manager in the product office for the specific product.

substance, intermediate, reagent, product component, drug product, container closure system, raw material or a combination of these, as appropriate)[36] and the material(s) that will be assessed in the tests and studies based on your risk assessment for the proposed change(s). The comparative assessment should be performed at commercial manufacturing scale, except where less than commercial scale is justified.[37] The projected number of batches, batch size or scale, site of manufacture, and manufacturing process to be used should be provided.

The selection of the relevant tests and studies to be performed should be scientifically justified and based on the risk assessment for the proposed change(s). You should confirm that the routine quality controls (e.g., conformance to specifications, meeting process controls, annual stability batch testing) will be appropriate to ensure continued product quality after implementation of the CMC change(s). However, routine quality controls alone are generally not considered adequate to assess the impact of CMC changes since they are chosen to confirm the routine quality of the product rather than to fully characterize it. In addition to the routine quality controls, relevant characterization and other tests and studies (e.g., structural characterization, impurities characterization, comparative multipoint dissolution profiles, extractables/leachables studies, biological characterization, stability studies, as appropriate) to assess the potential effects of the proposed change(s) and to ensure continued product quality should be specified in the CP. A plan for comparison of impurity profiles before and after a change should be included, as appropriate. Stability studies (e.g., long-term, accelerated, forced degradation), when needed, should provide a comparison of products manufactured before and after the change(s) to ensure that the product will maintain quality throughout its shelf life after implementation of the proposed change(s). Any other studies based on your risk assessment also should be included, where appropriate.

Analytical procedures should be described in the CP or incorporated by reference if previously submitted in your application. The analytical procedures should be capable of providing the information needed to assess the effects of the proposed change(s) and ensure product quality. Information to support that the analytical procedures are appropriate for their intended purpose also should be provided or incorporated by reference. You should use analytical procedures, sampling methodologies, and statistical methods, where appropriate, that provide a scientifically valid assessment of product quality.[38] Such procedures can include online determinations and statistical analysis. Data analysis methods and their selection and development should be described, including statistical methods to be used.

Acceptance criteria to be achieved that ensure the quality of the product after implementation of the CMC change(s) should be specified in the CP. You should confirm that the acceptance criteria established for routine quality controls are appropriate for the CP. In addition to acceptance criteria for routine quality controls, relevant acceptance criteria to be achieved demonstrating that the change(s) was successful should be specified for each characterization test and study. You should include acceptance criteria related to the success of the change(s) for

[36] See footnote 19 and ICH Q7 and ICH Q11.
[37] Analysis of commercial scale batches should be included for implementation to assess the effect of the change on the product, except where not feasible (e.g., viral clearance studies). Other studies at less than commercial scale can be submitted as supporting information (see section IV.C.).
[38] You must comply, as applicable, with 21 CFR 211.160.

impurity profiles, stability studies, and any other studies, where applicable. Acceptance criteria may also include statistical analysis, such as analysis of data for trends and/or analysis of variability to ensure the continued quality of the product. If the acceptance criteria for the change(s) allow for differences in product quality attributes, you should provide justification based on your assessment of the effect(s) of the change(s) on safety and effectiveness. If you anticipate such differences, they should be prospectively described.

For a CP that includes a proposed specification change, the CP should provide for a comparison of the approved and proposed specifications to demonstrate that the proposed specification will provide the same or greater assurance of product quality as the current specification.[39]

For changes that can be made repeatedly using the CP, you should design the CP in such a way to ensure that the effects of such cumulative changes will not result in an unintentional drift in product quality over time.

For changes to biological products, you should describe the appropriate validation studies, if any, to be completed and the acceptance criteria to be achieved.[40]

### E. Proposed Reduced Reporting Category

FDA recommends that you propose an appropriate reduced reporting category (i.e., CBE-30 supplement, CBE-0 supplement, or annual report) for each CMC change to be implemented. FDA evaluates the proposed reporting category as part of its review of the CP submission and communicates any concerns about the proposal. FDA approval of the submission containing the CP includes your proposed reporting category, if justified, for each of the specified changes.

A change that would ordinarily be reported in a PAS would typically be reduced to either a CBE-30 or CBE-0 supplement using an appropriately designed CP. A change that would ordinarily be reported in a CBE-30 or CBE-0 supplement would typically be reduced to annual report using an appropriately designed CP.

However, for certain changes, a reduced reporting category may not be justified (e.g., certain manufacturing site or other manufacturing changes that require a facility evaluation[41] and preapproval inspection; certain major changes to difficult to characterize products). See the Appendix for additional examples and further details.

In certain cases, because the complexities associated with the change(s) result in an unacceptably high or uncertain risk to product quality for that specific product, the FDA may determine that the change(s) should be reported in a regular PAS, rather than using a CP (see Appendix).

---

[39] See ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (November 2005) (ICH Q2(R1)), FDA guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015), and the Appendix for further details.

[40] For required validation and/or other clinical and/or nonclinical laboratory studies see 21 CFR 601.12(a)(2); for the submission of protocols describing the specific tests and validation studies, see 601.12(e). See also footnote 27.

[41] In this guidance document, the terms "facility" and "establishment" are synonymous (see the definitions for "establishment" in 21 CFR 207.1 and 600.3).

### F. Other Information

FDA recommends that you indicate, when possible, whether the CP is for a one-time change(s) or for repeated use for a specified type of change over the life cycle of the product.

The CP should provide confirmation that the site will not distribute product manufactured with the change(s) until the site's quality control unit has confirmed that the acceptance criteria specified in the protocol have been achieved and has approved the implementation of the change.

An estimated timeline for implementation of the change(s) should be provided, if available (e.g., for a specifically planned one-time change).

## V. MODIFICATIONS TO AN APPROVED COMPARABILITY PROTOCOL

According to 21 CFR 314.70(e) and 601.12(e), any proposed modification to an approved CP must be submitted as a PAS. However, notwithstanding these requirements, this guidance provides for a less burdensome notification of certain types of modifications to an approved CP as provided for in 21 CFR 314.70(a)(3) and 601.12(a)(3), to make CPs more useful and flexible, and to facilitate keeping CPs current.

The following are examples of modifications to an approved CP considered to have a moderate potential to have an adverse effect on product quality. If these planned modifications fit within the scope (e.g., same type of change(s)) of the original CP submission, they must be submitted as a CBE-30 supplement unless they otherwise fall within a lower reporting category pursuant to this section:

- Replacement or modification of a characterization test or study as specified in an approved CP that provides the same assurance of the product quality,

- Change in an acceptance criterion to be achieved for a characterization test or study as specified in an approved CP that provides the same assurance of the product quality, and

- Inclusion of an additional approved application in a previously approved CP for an identical CMC change(s) that affects multiple applications.

The following are examples of modifications to an approved CP considered to have a moderate potential to have an adverse effect on product quality. If these planned modifications fit within the scope (e.g., same type of change(s)) of the original CP submission, they must be submitted as a CBE-0 supplement unless they otherwise fall within a lower reporting category pursuant to this section:

- Replacement or modification of a characterization test or study as specified in an approved CP that provides increased assurance of the product quality, and

- Addition of a characterization test, study, or associated acceptance criterion to be achieved not specified in an approved CP that provides the same or increased assurance of the product quality.

The following are examples of modifications to an approved CP considered to have a minimal potential to have an adverse effect on product quality. If these planned modifications fit within the scope (e.g., same type of change(s)) of the original CP submission, they must be submitted in an annual report:

- Any change to a characterization test or study, analytical procedure, or acceptance criteria to be achieved as specified in an approved CP that is made to comply with an official compendium and that does not relax an acceptance criterion or delete a test,

- Tightening of acceptance criteria to be achieved for a characterization test or study,

- An approved change in the information within the application that is referenced in an approved CP, and

- Editorial changes to an approved CP.

This section of the guidance has a binding effect with regard to submitting such modifications to an approved CP in a CBE-30 supplement, CBE-0 supplement, or annual report rather than a PAS.

For tracking purposes, FDA recommends that a submission proposing modifications to an approved CP include a reference to the previously approved original application or PAS supplement containing the CP. The appropriate FDA review division can be contacted for questions regarding proposed modifications to an approved CP for a specific product.[42]

## VI. IMPLEMENTATION OF CMC CHANGES ACCORDING TO AN APPROVED COMPARABILITY PROTOCOL

When making a CMC change(s) in accordance with an approved CP, you should review the initial risk assessment associated with making the change(s) provided in the approved CP and compare it with your current understanding of the product and manufacturing process to ensure that the outcomes of that risk assessment as they pertain to the planned change(s) remain valid. If your review of the risk assessment indicates a substantive difference in the previously described level of risk associated with making the change, either higher or lower, this may affect the reporting category for the change(s) specified in the approved CP. In this case, we recommend that you contact the appropriate FDA review division to discuss an appropriate course of action, which may include modification of the CP, the approved reporting category, or both. In addition, you should confirm that your control strategy will continue to ensure

[42] For questions about a CP submitted to an approved NDA, ANDA, or BLA in CDER, contact the Regulatory Business Process Manager in OPQ for the specific product. For questions about a CP submitted to a BLA, NDA, or ANDA in CBER, contact the Regulatory Project Manager in the product office for the specific product.

consistent production of product of acceptable quality after implementing the change(s). The change(s) outlined in the approved CP should be implemented within your change management system as part of your overall pharmaceutical quality system.[43] In addition, the change(s) must be approved by your quality control unit.[44] Upon completion of the plan for successful implementation of the change(s) as described in the approved CP (including achievement of all of the predefined acceptance criteria), the change(s), if implemented, must be submitted to FDA using the reporting category specified in the approved CP submission.[45]

FDA realizes that minor deviations from the approved CP may occur during implementation. Such deviations should not affect the technical principles of the protocol, should be addressed by the risk assessment, and should not affect product quality or the approved reporting category. You should evaluate whether the CP needs to be modified (see section V).

You are responsible for ensuring that the facility(ies) where the change(s) is to be made is capable of implementing the change(s) in accordance with CGMP. If any impacted facility is not capable of implementing the change(s) in accordance with CGMP, the approved CP should not be implemented at those facilities.[46]

In addition, CGMP observations that raise concern regarding the effectiveness of a facility's pharmaceutical quality system, and change management in particular, may lead to a need to modify previously approved CP reporting categories until the pharmaceutical quality system effectiveness has returned to an acceptable state. For example, inspection observations that lead to classifying a facility as Official Action Indicated (OAI) would generally impact an approved CP. In these cases, FDA intends to communicate with facilities and applicants, as appropriate, any CP reporting category modifications that are necessary based on CGMP observations, which may include reverting to the reporting categories that would apply in the absence of the approved CP.[47]

You should collect and analyze commercial scale data, except where less than commercial scale data is justified,[48] to determine whether the change(s) has been successfully implemented in accordance with the approved CP.

Data demonstrates criteria have been achieved

If the data derived from the tests and studies demonstrate that the approved acceptance criteria in the CP have been achieved, the product manufactured by the new process can be distributed once the provisions of the approved reporting category are satisfied (e.g., if a PAS, after approval is

[43] See ICH Q10*,* section II.B.
[44] See footnote 17.
[45] See 21 CFR 314.70 and 601.12.
[46] In the case where a manufacturing change is needed to correct a CGMP deficiency, we recommend that you contact the appropriate FDA review division regarding how to proceed.
[47] See ICH Q12. For additional discussion of inspection observations that raise concern regarding the effectiveness of the pharmaceutical quality system, see draft guidance for industry *ICH Q12: Implementation Considerations for FDA-Regulated Products* (May 2021). When final, this guidance will represent FDA's current thinking on the topics therein.
[48] See footnote 37.

obtained; if CBE-30, 30 days after notification; if CBE-0, upon notification; if an annual report, distribution can commence immediately).[49]

Following implementation of the change(s), you must continue monitoring the process performance and product quality in accordance with CGMP requirements to ensure that a state of control is maintained.[50] Written records, including records containing the data associated with implementing the change(s), must be retained in accordance with CGMP requirements (see 21 CFR 211.180(e)). These records (or copies of such records), including the raw data therein, must be available during the retention period[51] for FDA to review during an inspection under section 704(a)(1) of the FD&C Act or when requested by FDA in advance of or in lieu of an inspection as described in section 704(a)(4) of the FD&C Act. The data should be incorporated as part of your systematic approach to knowledge management[52] to inform future product and process development.

Data demonstrates criteria have not been achieved

If the data derived from the tests and studies demonstrate that the approved acceptance criteria in the CP have not been achieved or there is an otherwise unwanted, unintended, or unpredicted outcome that affects product quality,[53] product manufactured by the altered process must *not* be distributed.[54]

If you wish to pursue such a change using a CP, FDA recommends that you contact the appropriate FDA review division to discuss an appropriate course of action, which may include modification of the proposed change(s) as well as the risk assessment, the CP for the change, and the reporting category. Alternatively, you may choose to pursue such a change without using a CP; in that case, the proposed change(s) must be reported using the applicable reporting categories established in 21 CFR 314.70 or 601.12.[55] If you determine that an approved CP will not be used to make a change, FDA recommends that you request withdrawal of the approved CP in a CBE-0 supplement to your application.

## VII. REPORTING CMC CHANGES MADE IN ACCORDANCE WITH AN APPROVED COMPARABILITY PROTOCOL

As required by 21 CFR 314.70, you must notify FDA about each change in each condition established in the approved application beyond the variations already provided for in the

[49] In addition to satisfying the provisions of the approved reporting category, successful completion of Stage 2 process validation is also necessary before commercial distribution (see 21 CFR 211.22, 211.100, and 211.165). See also guidance for industry *Process Validation: General Principles and Practices* (January 2011).
[50] See 21 CFR 211.100. See also the recommendations in ICH Q10.
[51] See section 704 of the FD&C Act (21 U.S.C. 374) and 21 CFR 211.180.
[52] See ICH Q10.
[53] For example, differences are observed in product quality attributes between the pre-change and post-change products and the impact on safety and/or efficacy profiles of the product cannot be excluded without performing a nonclinical safety, pharmacokinetic/pharmacodynamic, or clinical safety or efficacy study to assess the effects of the change(s) (e.g., see ICH Q5E).
[54] See section 506A(b) of the FD&C Act, and 21 CFR 314.70 and 601.12.
[55] See footnote 31.

application. You must notify FDA about these changes in a supplement or annual report as described in 21 CFR 314.70(b)-(d). As required by 21 CFR 601.12, you must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s).

However, with an approved CP, upon successful completion of the plan for implementation of the change(s) as described in the CP (including achievement of all of the predefined acceptance criteria for success in the approved CP), you must notify FDA of the change(s) using the reporting category specified in the approved CP.[56] The submission should include all of the information agreed upon in the approved CP. The level of detail of the information provided should be commensurate with the change(s) and reporting category. The submission should update, using the ICH CTD-Q format[57] (where applicable), the appropriate section(s) of the application to which the CMC change(s) applies. The submission should begin with a descriptive heading that identifies the change(s) as being made in accordance with an approved CP and should include the following:

- For tracking purposes, a reference to the previously approved original application or PAS containing the CP, and any previously approved modifications to the CP (see section V).

- A statement that all approved acceptance criteria in the CP for the findings have been achieved and that the change(s) was successfully implemented (for CBE-0 or annual report reporting categories) or will be implemented (for PAS or CBE-30 reporting categories) under the site's pharmaceutical quality system, including approval by the quality control unit.

- Details regarding the implementation of the change(s), the data derived from the tests and studies (e.g., tables, graphs, representative chromatogram)[58] and your analysis. A side-by-side comparison of the data should be presented, if applicable.

- Update of the risk assessment provided with the approved CP submission (if any), or a statement that risk assessment has not changed.

  As indicated above, if the updated risk assessment indicates a substantive change in the level of risk associated with the change, this may impact the previously approved CP, reporting category, or both (see section VI).

- A summary, including justification, of any minor deviations from the approved protocol and associated investigations performed (see section VI).

- Conclusions reached after your assessment of the overall effect of the change(s) on product quality.

[56] See 21 CFR 314.70 and 601.12.
[57] See ICH M4.
[58] The underlying raw data should not be submitted unless specifically requested by FDA.

Any new information regarding the change(s) that is generated after implementation should be included in the next annual report (e.g., stability data).

## VIII. LIST OF ABBREVIATIONS

The following is a list of abbreviations used in this guidance:

| | |
|---|---|
| ANDA | abbreviated new drug application |
| BCS | biopharmaceutics classification system |
| BLA | biologics license application |
| CBE-0 | changes being effected |
| CBE-30 | changes being effected in 30 days |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CGMP | current good manufacturing practice |
| CMC | chemistry, manufacturing, and controls |
| CP | comparability protocol |
| CQA | critical quality attribute |
| CTD-Q | common technical document - quality |
| DMF | drug master file |
| FDA | Food and Drug Administration |
| FD&C Act | Federal Food, Drug, and Cosmetic Act |
| ICH | International Council for Harmonisation |
| IVIVC | in vitro/in vivo correlation |
| IND | investigational new drug application |
| IR | immediate release |
| MR | modified release |
| NDA | new drug application |
| PACMP | postapproval change management protocol |
| PAS | prior approval supplement |
| PAT | process analytical technology |
| SS | semisolid |
| SUPAC | scale-up and postapproval changes |
| USC | United States Code |

## APPENDIX - QUESTIONS AND ANSWERS ON COMPARABILITY PROTOCOLS

### A. General

*1. What kinds of CMC postapproval changes are considered suitable for a CP submission?*

Many types of CMC changes in the drug substance, product, production process, quality controls, equipment, or facilities that would ordinarily require submission of a supplement[59] are considered suitable for inclusion in a CP submission (see sections B-J below).

*2. What kinds of CMC postapproval changes are considered not suitable for a CP submission?*

Changes that are considered not suitable for inclusion in a CP include those that would likely result in an unacceptably high or uncertain risk to product quality.

In general, FDA does *not* recommend a CP for the following:

- Unspecified plans for CMC changes (e.g., "to modify the manufacturing process")
- Changes to products that are difficult to characterize where the effect on product quality cannot be determined by prospectively defined tests, studies, analytical procedures, and acceptance criteria
- Changes that would need supportive data derived from a nonclinical safety, pharmacokinetic/pharmacodynamic, or clinical safety or efficacy study to assess the effects of the change(s) (e.g., toxicological study to evaluate new impurities, in vivo bioequivalence study to evaluate certain formulation changes)[60]
- Changes that require modification of the approved labeling with regard to the safety or efficacy of the product
- Change of a drug substance supplier to one that does not already supply drug substance used in the manufacture of an FDA-approved drug product
- Changes where the submission of an IND is needed[61]

[59] See 21 CFR 314.70 and 601.12.

[60] See the ICH guidances *Q3A(R2) Impurities in New Drug Substances* (June 2008) (Q3A(R2)), *Q3B(R2) Impurities in New Drug Products* (July 2006) (Q3B(R2)), SUPAC-IR, SUPAC-MR, and ICH Q5E. For information on a waiver of a bioequivalence study based on biopharmaceutics classification system (BCS), in vitro/in vivo correlation, or other acceptable approaches, see 21 CFR 320.22 and relevant guidances (e.g., *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021) (ICH M9) and *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997)).

[61] See 21 CFR part 312.

There are circumstances in which it might be possible to design and submit a CP for these types of CMC changes, but a reporting category other than PAS for changes implemented using such a protocol would generally not be justified because the complexities or uncertainties associated with the change(s) result in too high or uncertain risk to product quality for that specific product. In these cases, a CP might still be useful to gain agreement with FDA on the data needed to support a change, but otherwise, FDA recommends the use of a standard approach (e.g., submission of a PAS).

*3. Can I submit multiple CPs in my original application or in a PAS?*

You can submit one or more CPs with your original application to address postapproval CMC change(s).

For an approved application, if you are submitting more than one CP for unrelated changes, a PAS should be submitted for each CP. However, if more than one CP is needed to address multiple related changes (e.g., a site change that involves equipment and/or manufacturing process changes, multiple changes to a purification process, a formulation change that involves a specification change), FDA recommends that these CPs be submitted in the same PAS.

For multiple CP submissions in an original application or in a PAS to an approved application, where there is a possibility that the changes outlined in the multiple CPs could have an impact on each other, you should provide an assessment of the risk of such an impact. As a scientific matter, additional studies or testing may be needed to assess the combined effect of multiple changes on product quality. Where relevant, you also should indicate the sequence for implementing the change(s). In some cases, it may be useful to contact the appropriate FDA review division before submitting such CPs.

*4. Can I submit a single CP with multiple CMC changes?*

Multiple, related CMC changes that are intended to be implemented simultaneously or in a concerted manner can be submitted in a single CP. A justification should be provided showing how the changes are related and how including the multiple changes in a single CP is appropriate. Such changes can result in combined effects that might not be anticipated when considering the individual changes alone. You should address the risk of potential adverse effects as a result of such multiple changes in the supporting information for such a CP.

*5. Can one or more CMC changes that apply to multiple products be covered in a single CP?*

A single CP can be used for one or more proposed CMC changes that apply to multiple products marketed by the same applicant (e.g., a change in the manufacture of a drug substance used in multiple products, a change in the facility used for manufacturing multiple products, a change in an analytical procedure, a change to the container closure system used for multiple products).[62] Such CP should include the plans for reporting data that is applicable to all of the affected

[62] In this situation, a lead application can be used for submission of the CP and other affected applications can cross reference to the CP in the lead application. See 21 CFR 314.50(g)(1).

applications (product-wide data) as well as data that apply to each of the individual affected applications (product-specific data), as applicable. For submission of a single CP to be appropriate, the risk of the proposed change(s) should be similar across the multiple products. For submission of such a CP for an identical CMC change(s) that applies to multiple products marketed by the same applicant (e.g., grouped supplements, trans-BLA), we recommend that you contact the FDA review division for your lead (primary) application in the group of affected applications for questions on the appropriate content and format of the submission(s).[63]

*6. What are FDA's recommendations regarding CPs for CMC changes that can be made repeatedly over the life cycle of a product?*

A CP can be designed to be used repeatedly for a specific type of CMC change over the life cycle of a product. You should address the risk of adverse effects on product quality as a result of such cumulative changes over time in the supporting information for the CP. The CP should be designed in such a way to ensure that the effects of such cumulative changes will not result in an unintentional drift in product quality over time. Also, you should reevaluate the CP before each use to ensure that it remains scientifically sound. A notification using the reporting category specified in the approved CP must be submitted to the application each time a change is implemented according to the approved CP.[64] Each notification should include the data to demonstrate that all of the predefined acceptance criteria in the approved CP for successful implementation of the change were met.

*7. Under what circumstances would FDA not approve a submission containing a CP?*

FDA does not intend to approve a submission containing a CP if, after substantive review, we find the CP deficient.[65] FDA may, for example, find the CP deficient if:

- The proposed CMC change, if implemented, is likely to result in an adverse effect on product quality.
- The type of change is not specified in sufficient detail to permit identification of the tests and studies to be performed, including analytical procedures to be used, and acceptance criteria to be achieved to demonstrate the lack of adverse effect of the change on product quality.
- Each of the tests and studies to be performed, including analytical procedures to be used, and acceptance criteria to be achieved to demonstrate the lack of adverse effect of the change(s) on product quality, is not specified.

[63] See CDER MAPP 5015.6: *Review of Grouped Product Quality Supplements* and CBER SOPP 8422: *Processing of Trans-BLA Submissions*.
[64] See 21 CFR 314.70 and 601.12.
[65] See 21 CFR 314.70(e) and 601.12(e). Deficiencies are communicated in an information request, a discipline review letter, or a complete response letter. See FDA guidances for industry *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act* (November 2001) and *Information Requests and Discipline Review Letters Under GDUFA* (January 2022).

- The proposed tests, studies, and acceptance criteria to be achieved are not scientifically sound and/or appropriate for their intended purpose to ensure that the proposed CMC change(s) would not adversely affect product quality.

- The tests and studies to be performed are considered insufficient, and a nonclinical safety, pharmacokinetic/pharmacodynamic, or clinical safety or efficacy study would be needed to demonstrate the lack of adverse effect of the change(s) on product quality.

- Insufficient supporting information is provided to reasonably predict whether the proposed CMC change(s) would be likely to have an adverse effect on product quality.

- Insufficient information is provided to justify the proposed reduced reporting category for notifying FDA about the proposed change(s).

*8. Can I submit a modification to an approved CP together with a report of a CMC change(s) from the modified CP?*

Yes. In this case, FDA should be notified in accordance with the most restrictive postapproval submission category that applies to either the CP modification (see section V) or the reporting category for the CMC change(s) from the modified CP.

### B. Formulation (Component and/or Composition) Changes

*Can I include formulation (component and/or composition) changes in a CP?*

Formulation changes that can be evaluated using in vitro studies without the need for an in vivo bioequivalence study may be considered suitable for a CP.[66] A CP could also be useful for changes where you have sufficient data from a previously completed bioequivalence study and/or waiver of a bioequivalence study based on a biopharmaceutics classification system,[67] in vitro/in vivo correlation (IVIVC),[68] or other acceptable approaches that support the proposed changes. Formulation changes should be supported by relevant pharmaceutical development information.

### C. Facility Changes

*Can a CP be used for a change in the location of an operation to a different facility?*

Changes in the location of an operation to a different facility can be proposed in a CP, but because these changes will generally involve a facility evaluation, they generally do not justify a

[66] See SUPAC guidances listed in footnote 19 for recommendations about when bioequivalence studies should be conducted for postapproval formulation changes.
[67] See ICH M9.
[68] See FDA guidance for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997).

reporting category other than a PAS or CBE-30 supplement. Such facility evaluations may include factors such as the facility's prior inspection history, prior manufacturing experience with the dosage form that is the subject of the change, and the effectiveness of the facility's pharmaceutical quality system. This type of evaluation cannot be effectively conducted at the time of the CP submission, because certain factors at the time the change is to be implemented may be different from those at the time the CP is submitted. Based on this evaluation, FDA may determine that an inspection of the proposed facility is needed before making a decision on the supplement's approvability. In addition, for products that are difficult to characterize, site changes are more likely to need a preapproval inspection and therefore, in many cases, a reporting category lower than PAS would not be justified.

If the facility is not currently operating in an acceptable state of compliance with CGMP for the type of operation subject to the change, a PAS will be necessary to gain approval for the facility change and any associated manufacturing process changes. If a CBE-30 supplement is submitted in this situation to report the change(s) instead of a PAS, for NDAs and BLAs, FDA may convert the submission to a PAS absent any action by the applicant. For ANDAs, the applicant is notified to resubmit the CBE-30 as a PAS.[69]

However, changes that involve the addition of or move to a new facility would generally not be considered suitable for a CP if these changes need to be supported by an in vivo bioequivalence study.[70]

### D. Manufacturing Process Changes

*1. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that may affect the structure of the drug substance?*

In general, your CP should include appropriate structural characterizations, analytical procedures to be used, and acceptance criteria to be achieved to demonstrate the lack of adverse effect on product quality from manufacturing process changes that may affect the structure of the drug substance. Depending on the type and complexity of the drug substance, functional characterization studies should also be included. For example:

- For chemical drug substances, you should include appropriate structural characterization, analytical procedures to be used, and acceptance criteria to be achieved to ensure that the chemical structure remains unchanged in a CP for any manufacturing process change that could affect the chemical structure (e.g., stereochemical configuration) of the drug substance (e.g., change in route of synthesis or manufacturing process).

- For recombinant DNA-derived protein products, certain manufacturing process changes (e.g., change in biosynthesis/bioreactor conditions) could affect the structure

[69] See FDA guidance for industry *ANDA Submissions – Prior Approval Supplement under GDUFA* (October 2017).
[70] For example, in accordance with the guidance SUPAC-MR, a change in manufacturing site to a different campus should be supported by documentation from a bioequivalence study or waiver of such study based on an established in vitro/in vivo correlation (IVIVC). See also footnote 60 regarding a waiver of a bioequivalence study.

(e.g., amino acid substitution, post-translational modifications) of the drug substance. Therefore, you should include appropriate comparative structural (e.g., primary and higher order structure, glycan profiles) and functional characterization (e.g., biological activity, binding assay), analytical procedures to be used, and acceptance criteria to be achieved to demonstrate that the products before and after the change(s) are analytically comparable.[71]

- For products that are difficult to characterize, we recommend that you contact the appropriate FDA review division regarding manufacturing process changes that may affect the structure of the drug substance.

*2. Does FDA have any recommendations about what to include in a CP for manufacturing process changes that may affect the physical properties of the drug substance?*

You should include a comparison of the properties of the drug substance before and after the change in a CP for a manufacturing process change that could affect the physical properties of the drug substance (e.g., morphic forms, particle size). You may also choose to demonstrate the suitability of the drug substance for use in the manufacturing of the product. Regardless of the approach taken, it is important in this situation to describe and assess how the change(s) is not expected to adversely affect the quality, bioequivalence, and the clinical performance of the product. However, changes that affect the physical properties of the drug substance that need to be supported by an in vivo bioequivalence study would generally not be considered suitable for a CP (see question and answer A.2).

*3. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that could affect the impurity profile?*

A CP for manufacturing process changes should include a specific plan to determine any qualitative and quantitative changes to the impurity profile of the drug substance, drug substance intermediate, in-process material, other material, and/or product manufactured using the new process. You should demonstrate an understanding of the origin and risk of any new or increased level of impurities or contaminants. The CP should specify the step(s) in the manufacturing process where you will measure and control the impurity profile. The analytical procedures utilized should be capable of detecting, identifying and/or quantitating new impurities or other differences in the product that could result from the change (see section IV.D).

For products derived from a biological source, the CP should include an assessment of the capability of the manufacturing process to remove or inactivate virus and/or other adventitious agents; viral and adventitious agents screening; and assessment of potentially immunogenic impurities (e.g., host cell proteins, aggregates), as applicable.

[71] See ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (August 1999) (ICH Q6B) and ICH Q5E.

Changes that need to be supported by a toxicology study to evaluate new impurities and/or an in vivo immunogenicity study would generally not be considered suitable for a CP (see question and answer A.2).

*4. Does FDA have any recommendations or issues for industry to consider regarding changes to manufacturing process controls in a CP?*

In cases where a proposed CP provides for modified or new manufacturing process controls, such modified or new controls should be suitable for their intended purpose and provide the same or increased control when compared to the current process controls. The modified or new manufacturing process controls should be sufficiently described and justified so that the assurance of product quality can be ascertained.

*5. Can a CP be used for a wide range of potential parameter changes to a manufacturing process?*

An appropriately designed CP can be used to provide for a wide range of potential process parameter changes to a manufacturing process using a risk-based approach, if you have a high level of product and process understanding. A risk assessment should be conducted on the potential for product and/or intermediate critical quality attributes (CQAs) to be affected by parameter changes. An understanding of process robustness can be useful in risk assessment and risk reduction.[72] You should also consider the impact to the overall quality target product profile (QTPP) as part of your life cycle management.[73] In many cases, it may be possible to group parameter changes by individual unit operation or groups of unit operations. The specific tests and studies proposed to evaluate the changes should address how quality can be assured for the product, including product and/or intermediate CQAs.

Often, pilot or smaller scale data can be used to identify the potential risks to product quality and help inform development of a suitable evaluation plan. The risk assessment should consider how multiple manufacturing parameter changes can result in combined effects that might not arise from individual parameter changes. The risk of adverse effects as a result of such multiple changes should be addressed during manufacturing process development and included in the supporting information for the CP.

*6. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that may affect the in vitro release characteristics of the product?*

Manufacturing process changes that may affect the in vitro release characteristics of the product are considered suitable for a CP if they can be sufficiently supported by in vitro studies without the need for an in vivo bioequivalence study.[74] You should include in the CP appropriate

[72] See ICH Q8(R2) and ICH Q9.
[73] See ICH Q8(R2); ICH Q8, ICH Q9, & ICH Q10 Questions and Answers (November 2011); and ICH Q11.
[74] For example, according to guidance SUPAC-MR, a change from wet granulation to direct compression of dry powder should be supported by a bioequivalence study or waiver of such study based on an established in vitro/in vivo correlation. See also footnote 60 regarding a waiver of a bioequivalence study.

comparative in vitro release studies of the products before and after such manufacturing process changes. You should establish the adequacy of the comparative in vitro release studies to assess the effects of the change(s) without the need for an in vivo bioequivalence study.

*7. Does FDA have any recommendations for industry to consider regarding a CP for changes in manufacturing process scale?*

A CP can be useful for changes in manufacturing process scale (scale-up, scale-down, scale-out), where submission of a supplement would ordinarily be needed.[75] FDA recommends that you include information on potential effects of changes in manufacturing scale on product quality,[76] if available.

*8. Can a change from batch to continuous manufacturing be considered in a CP?*

The use of a CP can be considered for a change from batch to continuous manufacturing process. However, because a pre-approval inspection would likely be needed to implement continuous manufacturing, a reporting category other than a PAS would generally not be justified. A CP might still be useful for you to gain agreement with FDA on the data needed to support the change.

### E. Manufacturing Equipment Changes

*Does FDA have any recommendations for industry to consider regarding manufacturing equipment changes using a CP?*

An approved CP with a reduced reporting category can be useful for the proposed addition, modification, or replacement of manufacturing equipment that would otherwise require submission of a supplement thereby facilitating increased manufacturing flexibility. The CP submission should address any differences in equipment design, operating principles, and/or size, as applicable.[77]

### F. Specification, Including Analytical Procedure (Method) Changes

*Does FDA have any recommendations or issues for industry to consider regarding specification changes in a CP?*

Specifications are the quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or product.[78] Changes to

[75] See footnote 19 regarding guidances on postapproval CMC changes.
[76] See ICH Q8(R2); ICH Q10; ICH Q8, ICH Q9, & ICH Q10 Questions and Answers; and ICH Q11.
[77] See footnote 19 regarding guidances on postapproval CMC changes.
[78] See the definitions for "specification" in 21 CFR 314.3 and 600.3. See also ICH guidances for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000) (ICH Q6A) and ICH Q6B.

the approved specification that provide the same or greater assurance of product quality can be included in a CP. A CP submission for a specification change should include a justification for the change.

For replacement or modification of an existing analytical procedure in an approved application, the new procedure must be scientifically sound[79] and should provide the same or greater assurance of product quality than the currently approved procedure.[80] The CP should include the specific plan, description of statistical method(s) to be used, and acceptance criteria to be achieved for evaluating the performance of the new procedure. Method validation data should be submitted with the notification of the change.

A CP can also be used for replacing a quality reference standard used in an analytical procedure(s).

### G. Packaging Changes

*Does FDA have any recommendations or issues for industry to consider regarding packaging changes in a CP?*

You can use a CP for packaging changes. The CP can apply to components of the container closure system or their manufacturing processes. CPs for changes to multiple components of a container closure system should adequately address the potential effects of the interchangeability of container closure system components on product quality, where applicable.

### H. Process Analytical Technology Changes

*Does FDA have any recommendations regarding process analytical technology implementation or changes in a CP?*

You can propose the implementation of process analytical technology (PAT) or propose a change in PAT in a CP. Information on the suitability of a PAT tool on experimental and/or production equipment and processes can be submitted to support a CP for PAT implementation or change(s).[81]

### I. Changes to Drug-Device or Biologic-Device Combination Products

*Does FDA have any recommendations regarding changes to drug-device or biologic-device combination products in a CP?*

In general, a CP can be submitted for changes to a drug-device or biologic-device combination product where CDER or CBER is the lead center. The nature of the proposed change to the device constituent part would need to be considered in determining if a CP would be suitable.

---

[79] See 21 CFR 211.160.
[80] See ICH Q2(R1) and FDA guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (July 2015).
[81] See footnote 34.

For questions as to whether a CP would be suitable for a specific drug-device or biologic-device combination product, we recommend that you contact the appropriate FDA review division.

## J. Master Files

*1. Can a drug master file (DMF) be cross-referenced in a CP that is included in an application submitted under section 505 of the FD&C Act?*

In an application approved or seeking approval under section 505 of the FD&C Act, a DMF can be cross-referenced[82] in a CP that provides for postapproval CMC changes (e.g., addition of a supplier of a drug substance used in an FDA-approved drug product, a change in an excipient supplier, a change in the supplier of a container and/or closure). The CP should indicate the type of CMC information that will be incorporated by reference to the DMF. Also, the CP should include the tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the suitability of the material supplied by the DMF holder (e.g., conformance to approved specification, compatibility studies, stability studies). We recommend that the CP submission specify that a copy of the letter authorizing incorporation by reference of the information in the DMF will be provided when reporting a postapproval CMC change implemented using the approved CP to FDA. If the subsequent submission notifying FDA of the postapproval CMC change does not include the letter of authorization, the notification to FDA would be incomplete. The applicant is responsible for ensuring that the DMF holder's methods, facilities, and controls relevant to the change are in accordance with CGMP. A CP for a change in drug substance supplier is generally not recommended if the proposed change is to a drug substance supplier that does not already supply drug substance used in an FDA-approved drug product (see question and answer A.2).

*2. Can a master file be cross-referenced in a CP that is included in an application submitted under section 351 of the PHS Act?*

In general, in an application approved or seeking approval under section 351 of the PHS Act, a master file, including a DMF, can be cross-referenced[83] in a CP that provides for postapproval CMC changes (e.g., changes to the information about excipients or materials used in the preparation of drug substance, drug substance intermediate, or drug product), except if the information in the master file is drug substance, drug substance intermediate, or drug product information. The CP should indicate the type of CMC information that will be incorporated by reference to the master file. Also, the CP should include the tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the suitability of the material supplied by the master file holder (e.g., conformance to approved specification, compatibility studies, stability studies). We recommend that the CP submission specify that a copy of the letter authorizing incorporation by reference of the information in the master file will be provided when reporting a postapproval CMC change implemented using the approved CP to FDA. If the subsequent submission notifying FDA of the postapproval CMC change does not include the letter of authorization, the notification to FDA would be incomplete. The applicant is responsible for

[82] See 21 CFR 314.420.
[83] See 21 CFR 601.51.

ensuring that the master file holder's facilities, methods, and controls relevant to the change are in accordance with CGMP.

*3. Can a CP be submitted to a master file?*

A CP for postapproval CMC changes can be submitted to a master file, including a DMF, by the master file holder. For example, a CP submitted to a master file may be useful to support changes affecting multiple applications. However, FDA neither independently reviews nor approves or disapproves submissions to master files; instead, FDA reviews a CP or other information in a master file only in connection with applications that incorporate by reference such information. Administrative considerations relating to reviewing CPs in master files can present some unique challenges; therefore, a master file holder should coordinate with FDA prior to submitting such a CP.[84]

[84] For questions about submission of a CP to a DMF in support of an NDA or ANDA, or to a master file, including a DMF, in support of a BLA in CDER, contact the Regulatory Business Process Manager in OPQ for the specific product. For questions about submission of a CP to a master file, including a DMF, in support of a BLA, or to a DMF in support of an NDA or ANDA in CBER, contact the Regulatory Project Manager in the product office for the specific product.