Comparability Protocols for Human Drugs and Biologics:

Chemistry, Manufacturing, and Controls Information

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Stephen Moore at 301-796-7579 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Pharmaceutical Quality/CMC

Revision 1

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Chemistry, Manufacturing, and Controls Information

Guidance for Industry

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*Contains Nonbinding Recommendations**

Draft — Not for Implementation

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Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. With the exception of the discussion regarding submission of changes to a comparability protocol in a changes being effected supplement,[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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to holders of applications for human drugs and biologics on implementing a chemistry, manufacturing, and controls (CMC) postapproval change through the use of a comparability protocol (CP). It replaces the draft guidance that published in February 2003, titled *Comparability Protocols: Chemistry, Manufacturing, and Controls Information.*

A 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 (i.e., product),[3] as these factors may relate to the safety or effectiveness of the product (i.e., product quality).[4] Submission of a CP in an original application or prior approval supplement (PAS) allows the agency to review a description of one or more proposed CMC postapproval changes, supporting information including any analysis and risk assessment activities, a plan to implement the change(s), and, if appropriate, a proposed reduced reporting category for the change(s). Approval of the original application containing the CP or a subsequent PAS containing the CP can provide an applicant with 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 the applicant's analysis of the data from the implementation of the change. In many cases, using 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 drug

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

[2] This limited portion of the guidance will have binding effect upon finalization, pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70.

[3] In this guidance, the term "product" refers to drug product and biological product (see 21 CFR 314.3 and 600.3) and to their constituent drug substances.

[4] In this guidance, the term "product quality" refers to product identity, strength, quality, purity, and potency, as these factors may relate to the safety or effectiveness of the product (see footnote 2).

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supply chain sooner than if a protocol were not submitted. This guidance is intended to establish a framework to promote continuous improvement in the manufacturing of quality products by encouraging applicants to employ:

- Effective use of knowledge and understanding of the product and manufacturing process
- A robust control strategy
- Risk management activities over a product's life cycle
- An effective pharmaceutical quality system

This guidance applies to CPs submitted to new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (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). The scope of this revised draft guidance does not include animal drugs.[5,6]

This guidance incorporates the modern regulatory concepts stated in FDA's guidance for industry on *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*,[7,8] the Pharmaceutical Current Good Manufacturing Practices for the 21st Century,[9] the Critical Path Initiative,[10] and the quality-by-design principles described in the International Conference on Harmonisation (ICH) guidance for industry on *Q8(R2) Pharmaceutical Development*. These principles are also incorporated in the following ICH guidances: *Q9 Quality Risk Management*, *Q10 Pharmaceutical Quality System*, and *Q11 Development and Manufacture of Drug Substances.*

[5] This guidance is not applicable to whole blood, blood components, and plasma, 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, and cellular and tissue-based products regulated solely under section 361 of the Public Health Service Act. Recommendations for the use of comparability protocols for licensed blood and blood components are included in a separate guidance, *Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture*.

[6] The Center for Veterinary Medicine, which was included in the first version of the draft guidance that published in February 2003, intends to publish recommendations for animal drugs in a separate guidance.

[7] This guidance is intended to provide 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, Good Guidance Practices, Level 2 Guidance – Products and Process Controls.*

[8] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or the FDA Biologics guidance page at www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[9] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836.

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

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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 guidances means that something is suggested or recommended, but not required. Insofar as section V of this guidance sets forth that certain modifications to an approved comparability protocol may be submitted in a changes being effected supplement rather than a prior approval supplement, it will have binding effect upon finalization.

II. BACKGROUND

As an NDA, ANDA, or BLA applicant, you are responsible for validating the effects of any 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 distributing the product made with the change.[11] 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 and 601.12. In those regulations, these postapproval CMC changes to established conditions 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 drug or biological product as they may relate to the safety or effectiveness of the product.[12] If a change has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug (a major change), an applicant must submit and receive FDA approval of a prior approval supplemental (PAS) application before the product made with the manufacturing change is distributed. If a change has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product, as these factors may relate to the safety or effectiveness of the drug (a moderate change), an applicant 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). If a change has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product, as these factors may relate to the safety or effectiveness of the drug (a moderate change) (a minor change), an applicant may proceed with the change, but must notify FDA of the change in the next annual report in accordance with 21 CFR 314.81 or 21 CFR 601.12(d), as applicable.

The regulations also provide for protocols as an optional way to manage postapproval changes.[13] A CP can be submitted in an original application or can be submitted as a PAS as provided for in 21 CFR 314.70(e) or 601.12(e).

[11] See section 506A of the FD&C Act, 21 CFR 314.70, and 21 CFR 601.12. A holder of an approved application under section 505 of the act 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, you are also 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)).

[12] See 21 CFR 314.70 and 21 CFR 601.12.

[13] See 21 CFR 314.70(e) and 21 CFR 601.12(e).

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Regardless of the type of change, the methods used and the facilities and controls used for the manufacture, processing, packaging, or holding of a drug must comply with current good manufacturing practices (CGMPs).[14] CGMPs provide for the implementation of oversight and controls over the manufacture of drugs 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.[15] All manufacturing and laboratory changes must be evaluated and approved by the quality control unit.[16] You are responsible 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.[17]

Other FDA and ICH guidances also discuss assessing and reporting of CMC postapproval changes[18] and CGMP.[19] 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. The description of the specific tests and studies to be performed should also include the analytical procedures to be used or reference thereto.[20] Analytical procedures include regulatory analytical procedures and those used for characterization studies.

A CP may be submitted as part of an original marketing application or can be submitted after approval of the original application as a PAS (a major change). The supplement containing the CP must be approved before distribution of a drug product produced with the change(s) as outlined in the protocol (see 21 CFR 314.70(e) and 601.12(e)). A CP, once approved, 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

[14] See sections 501 and 704 of the FD&C Act and 21 CFR 210.3(12). *Manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of products.

[15] The CGMP regulations for finished pharmaceuticals, at 21 CFR parts 210 and 211, and the biological product regulations at 21 CFR part 600, set the regulatory standard for manufacturing and quality control (note that 21 CFR parts 210 and 211 apply to licensed biological products that are regulated as drugs under the FD&C Act).

[16] For CGMP information on changes to products, see 21 CFR 211.22, 211.100, 211.110, 211.160, and 211.180.

[17] See 21 CFR 211.100, 211.110, 211.160 and 211.180(e) and International Council for Harmonisation (ICH) guidances for industry on *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7*)*, and *Q10 Pharmaceutical Quality System* (ICH Q10).

[18] For example, see FDA guidances *Changes to an Approved NDA or ANDA*, *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, *Immediate Release Solid Oral Dosage Forms*: *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* and *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*, *Analytical Procedures and Methods Validation for Drugs and Biologics*, and ICH *Q5E, Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process* (ICH Q5E).

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

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

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can also be submitted to cover an identical change(s) that affects multiple applications (grouped supplements, trans-BLA).[21]

A CP can be useful in providing predictability for applicants who anticipate the need to implement future changes to an approved product, including its manufacturing process. The drivers for such changes include business needs, expanding markets, process improvements, potential for drug shortage, and accelerated manufacturing development that occur with drugs subject to expedited programs.[22] 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. In addition, depending on the extent of available knowledge regarding the product and process, the associated risk of the proposed change(s), and the control strategy in effect, the Agency may be able to approve a protocol that justifies reporting certain changes in a manner not requiring approval from FDA prior to distribution of a product produced with the change (i.e., a CBE-type supplement or an annual report).

We recommend 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(s).

Your understanding should be derived from one or more of the following, as appropriate:

- Prior knowledge [23]
- Development of the drug substance and its manufacturing process[24]
- Pharmaceutical development (development of the product and its manufacturing process)[25]
- Process validation activities[26] and commercial-scale production experience
- Quality risk management activities[27]

[21] 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.

[22] See the guidance for industry on Expedited Programs for Serious Conditions – Drug and Biologics

[23] Prior knowledge can include established chemical and biological engineering principles, published, peer-reviewed scientific and technical literature, and applied manufacturing experience. Prior knowledge can be used at the beginning of development and assessments iteratively updated with development data (including data from nonclinical and clinical studies) during the life cycle. See ICH Q10.

[24] See the ICH guidance for industry on *Q11 Development and Manufacture of Drug Substances.*

[25] See the ICH guidance for industry on *Q8(R2) Pharmaceutical Development.*

[26] See the FDA guidance for industry on *General Principles of Process Validation.*

[27] See the ICH guidance for industry on *Q9: Quality Risk Management.*

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- Studies conducted at less than commercial scale to gain an increased understanding of the effects of the change(s) on product quality[28]

Seeking approval of a CP as part of the original application may facilitate the applicant's 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 analysis 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, the Agency intends to take into consideration the extent of the applicant's available process and product understanding, the potential risks associated with the proposed change(s), the control strategy, and the nature and extent of studies planned to support the change.

When you submit a CP to the Agency, we recommend that you give the CP a descriptive title, version number, and date for tracking purposes, and submit the CP in Module 3, section 3.2.R Regional Information. 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 that the reason for submission is "Comparability Protocol."

Once submitted by the applicant and approved by FDA, a submission containing a CP provides an applicant with an agreed-upon plan to implement the proposed change(s), and in many cases, justification to report the implementation of the propose change(s) in a reduced reporting category. Once approved, the CP serves as a commitment by the applicant to perform the specified activities outlined in the CP that can justify a reduced reporting category. Notification of the change(s) should be submitted using the reporting category specified in the approved CP submission if all of the predefined criteria for success in the approved CP have been met. If the activities specified in the approved CP are not performed or if the predefined criteria for success are not met, then any reduced reporting category is not justified and the change(s), if pursued, must be reported using the standard criteria established in 21 CFR 314.70, 601.12 and FDA guidances addressing postapproval changes.

IV. COMPARABILITY PROTOCOL SUBMISSION - CONTENT RECOMMENDATIONS

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

A. Summary

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

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We recommend that you provide a summary of the CP submission using tabular, narrative, or graphic representations, as appropriate. The summary should include a brief description of the following:

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

The detailed information described in sections B. though F. below should be provided in the CP submission.

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

The proposed change(s) should be described in sufficient detail to enable the Agency to evaluate the relevancy and adequacy of the CP. We recommend 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, and control strategy that are relevant to the proposed change(s).

The supporting information should include the following, as applicable:

- Prior knowledge to justify the proposed change(s)
- A summary of the risk assessment of the proposed change(s)

  This assessment should identify the potential effects of the change(s) on product quality.[29] 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.

[29] The extent of the risk assessment should be commensurate with the risk associated with the proposed change(s) and should be based on severity, probability, and detectability of potential effects on product quality.

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- Information from development of the drug substance and 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 of the product

  Development batches used to support the CP should be described according to batch size or scale, site and 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, application of statistically designed experiments and/or process analytical technology (PAT) can be used to gain such an understanding.

- Supporting information relevant to well-characterized recombinant DNA-derived products.[30]

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

D. Comparability Protocol for the Proposed Change(s)

The CP for the proposed change(s) should describe, in sufficient detail for FDA to assess the CP, the specific tests and studies to be performed, including analytical procedures to be used and criteria to be achieved, to demonstrate the lack of adverse effect on the product quality. These tests and studies should be performed at commercial manufacturing scale.[31] The CP should use a combination of both routine quality controls (e.g., specifications, process controls) and non-routine tests and studies (e.g., characterization tests and studies, stability studies). Increased sampling for these tests and studies may be appropriate. Criteria for the expected results should be established for each of these tests and studies. The level of detail that should be provided will depend on the complexity of the change and the specific risks associated with the change to product quality.

Comparative assessment of quality attributes before and after the change(s) should be included as a component of the planned tests and studies. A side-by-side comparison should be performed, if feasible. However, depending on the type of change, control strategy and level of risk, you can develop and implement a CP without such a comparative evaluation if, for example, the evaluation does not contribute to assurance of product quality. In addition, a side-by-side comparison can be a challenge when the control strategy is also being changed from one consisting primarily of final product testing to one that performs in-process testing to verify that the product has the desired

[30] See ICH Q5E.

[31] Commercial-scale batches should be used for implementation, except where not feasible (e.g., viral clearance studies).

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attributes. In this case, one approach would be to correlate the product attributes to one or more raw material attributes, in-process material attributes, or process parameters.

Characterization tests and studies are an essential part of an assessment of the effects of the proposed change(s) on product quality. You should provide scientific justification for the design of studies, selection of the tests, and analytical procedures and ensure they are capable of providing the information needed to assess the effects of the proposed change(s) and ensure product quality. Comparison of impurities profiles before and after a change should typically be performed. Stability studies (e.g., real condition, forced degradation), may also be appropriate and should provide a direct comparison of products manufactured before and after the change 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 plan also should be included, where appropriate.

Analytical procedures should be described in the CP or incorporated by reference to those previously submitted in your application. Information to support that the methods are appropriate for their intended purpose also should be provided. We encourage you to use analytical procedures, sampling methodologies, and appropriate statistical methods that provide a scientifically valid, statistical assessment of product quality, including product variability. Such procedures can include online determinations and statistical processing of data. Data analysis methods and their selection and development should be described, including statistical methods to be used.

Criteria that ensure the quality of the product after implementation of the CMC change(s) should be established and provided in the CP. Relevant and clearly defined acceptance criteria to be met demonstrating that the change was successful should be specified for each characterization test and study. You also should include acceptance criteria related to the success of the change for impurity profiles, stability studies, and any other studies, where applicable. Criteria also may include statistical trending or analysis of variability within specification limits. The acceptance criteria to be used for assessment should take into account your understanding of those aspects of the product, manufacturing process, control strategy, and risks that are relevant to the proposed change(s). The intended use of the product in the clinical setting should also be taken into account. The acceptance criteria for the change can allow for differences in product attributes if you provide justification based on your assessment of the effect(s) of the change on safety and effectiveness. If you anticipate such differences, they should be prospectively described.

E. Proposed Reduced Reporting Category

We recommend that you propose an appropriate reduced reporting category for implementation of each change (i.e., an annual report, CBE, or CBE-30). FDA will evaluate your proposed reporting category as part of its review of the CP submission and communicate any concerns about your proposal. FDA approval of the submission containing the CP will include your proposed reporting category, if appropriate, for each of the specified CMC changes.

However, for certain changes, a reduced reporting category may not be justified (e.g., where data from nonclinical safety, pharmacokinetic/pharmacodynamic, and safety and efficacy studies are needed to evaluate the effect of changes on product quality; future manufacturing site changes or

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certain other changes that warrant a facility evaluation and potential preapproval inspection). See the Appendix for additional examples and for further details.

In certain cases, the appropriate FDA review division may recommend submitting the change in a regular PAS rather than in a CP because the complexities associated with the change result in an unacceptably high risk to product quality for that specific product.

F. Other Information

We recommend that you indicate whether the CP is for a one-time change(s) or will be used repeatedly for a specified type of change over the life cycle of the product.

We also recommend that the CP provide that the site will not distribute product manufactured with the change(s) until the site's quality control unit has confirmed that the criteria specified in the protocol have been met and approved the implementation of the change. [32]

An estimated timeline for implementation of the change(s) should be provided, if applicable.

For biological products that are not specified biological products,[33] you should provide the qualification studies to be completed for new or modified manufacturing equipment and facilities, and the criteria to be met.

V. MODIFICATIONS TO AN APPROVED COMPARABILITY PROTOCOL

After submission and prior to approval of the original application or a PAS containing the CP, any proposed modification to the CP will be considered an amendment. After approval of the submission containing the CP, any modification to the CP must be submitted as a new PAS (see 314.70(e) and 601.12(e)).

Notwithstanding these requirements, as provided for in 21 CFR 314.70(a)(3), and 601.12(a)(3) to make CPs more useful and flexible, this guidance provides for a less burdensome notification of certain types of modifications to an approved CP. The following are examples of modifications to an approved CP that may be considered to have a moderate potential to have an adverse effect on the product quality. If these planned modifications are included in the scope of the original CP submission, they can be submitted as a CBE-30 supplement:

- Replacement or modification of a test, study or acceptance criterion specified in an approved CP that provides for the same or increased level of rigor of the CP for assessing the effect of the change(s) on the product quality

- Inclusion of an additional approved application in a previously approved CP which covers an identical change(s) that affects multiple applications[34]

[32] See footnote 15.
[33] See 21 CFR 601.2(a) 1-4.

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The following is an example of modifications to an approved CP that are considered to have a moderate potential to have an adverse effect on the product quality. If these planned modifications are included in the scope of the original CP submission, they must be submitted as a CBE supplement:

- Addition of a test, study, or acceptance criterion not specified in an approved CP that provides for the same or increased level of rigor of the CP for assessing the effect of the change(s) on product quality

Upon finalization of this draft guidance, submission of the modifications to an approved comparability protocol described above in a CBE-30 or CBE supplement rather than a prior approval supplement will be binding.

The appropriate FDA review division can be consulted for further advice on change(s) to an approved CP for a specific product on a case-by-case basis.

VI. IMPLEMENTATION OF CHANGES ACCORDING TO AN APPROVED COMPARABILITY PROTOCOL

When making a change(s) in accordance with the provisions of an approved CP, you should review the risk assessment provided in the initial CP submission and compare it with current knowledge to ensure that the outcomes of that risk assessment as they pertain to the planned change(s) remain valid. If the review of the initial 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 specified in the approved CP. In this case, we recommend that you contact the appropriate FDA review division because it may be necessary to modify the CP, the proposed reporting category, or both. In addition, you should confirm that your control strategy will continue to ensure that product will be produced consistently after implementation of the change(s). Finally, we expect that the change outlined in the approved CP will be implemented within your change management system as part of your overall pharmaceutical quality system.[35] You are responsible for ensuring that the facility(ies) where the change is to be made is capable of implementing the change in accordance with current good manufacturing practice (CGMP). For example, an "official action indicated" compliance status (see the FDA inspection classification database[36]) or issuance of an FDA warning letter to that facility can be indicative that the facility is not capable of implementing the change in accordance with CGMP. If any impacted facility is not capable of implementing the change in accordance with CGMP, the approved CP should not be implemented. If you still wish to make the change, you should follow applicable regulations and guidance, not the approved CP, to determine the appropriate reporting category for the change.

[34] See footnote 19.

[35] See 21 CFR Part 211 and guidances for industry on *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* and *Q10 Pharmaceutical Quality System*, section II. B.

[36] Available at http://www.accessdata.fda.gov/scripts/inspsearch/.

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If the approved criteria are met, product manufactured by the new process can be distributed once the provisions of the approved reporting category are satisfied (e.g., if a PAS, approval is obtained; if an annual report, distribution can commence immediately).

After a change(s) is made according to an approved CP for which the reporting category does not require prior approval, you should collect and analyze process validation and commercial-scale data to establish whether implementation of the change(s) has been successful (see section IV. D.).

If the data collected do not meet the approved criteria in the CP or there is an otherwise unwanted or unpredicted outcome, product manufactured by the altered process must *not* be distributed.[37] In addition, you should include a statement in the next annual report confirming that the change(s) has not and will not be implemented under the provisions of the CP. If you wish to pursue such change(s), you should contact the appropriate FDA review division to discuss an acceptable course of action.

Regardless of the reporting category in the approved CP, ongoing verification beyond that reported can and should be performed under your pharmaceutical quality system to continue to evaluate and ensure that there is a lack of adverse effect of the change(s) on product quality. The data associated with the implementation of the change(s) under a CP should be captured as part of your knowledge management system[38] to inform future product and process development; further, these data should be retained at the facility and be available for review by FDA at the Agency's discretion under CGMP.[39]

VII. REPORTING 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 application; for these changes you must notify FDA about the change in a supplement or by inclusion of the information in the annual report as described in 314.70(b)-(d). As required by 21 CFR 601.12, you must inform the 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, you can report the change(s) using the approved reporting category. The level of detail of the information provided should be commensurate with the change(s) and reduced reporting category. This submission should begin with a heading that identifies the change(s) as being made under an approved CP and should include the following:

[37] See section 506A(b) of the FD&C Act, 21 CFR 314.70, 21 CFR 601.12.
[38] See ICH guidance for industry *Q10 Pharmaceutical Quality System.*
[39] See section 704 of the FD&C Act and 21 CFR 211.

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- A reference to the number and date of approval for the approved original application or supplement containing the CP

- If the approved CP provided for a reporting category other than a PAS, a statement that all approved criteria for the findings were met and that the change(s) was successfully implemented under the site's pharmaceutical quality system, which includes approval by the quality control unit

- Details regarding the implementation of the change(s), a summary and analysis of the data (e.g., tables, graphs, charts), and any changes to the risk assessment

- Specific data if indicated to be necessary in the approved CP

- Update of the risk assessment provided with the approved CP submission (if any), or 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 reporting category. In this case, you should contact the appropriate FDA review division.

- Unexpected results that may have affected the tests or studies (if any)

- A summary of deviations and investigations performed (if any)

- Evaluation of the impact of the change on product quality

- Conclusions reached after evaluation of studies conducted to support the change

Any new information regarding the change(s) (e.g., stability data) that is generated after implementation should also be included in the next annual report. After a CP is approved, annual reports for each affected application should provide updates on the status of changes covered by the CP.

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APPENDIX - QUESTIONS AND ANSWERS ON COMPARABILITY PROTOCOLS

A. General

1. Are there chemistry, manufacturing, and controls (CMC) changes for which a comparability protocol is not recommended?

Yes. It would be inappropriate to use a comparability protocol (CP) for CMC changes that are likely to result in an unacceptably high or uncertain risk to product quality. In general, we do not recommend a CP for the following:

- Nonspecific plans for CMC changes (e.g., "to modify the manufacturing process")
- Changes where effect on product quality cannot be determined by defined studies, tests, analytical procedures, and criteria
- Changes where data from nonclinical safety, pharmacokinetic/pharmacodynamic, and safety and efficacy studies are needed to assess the effects of the change
- Changes that require modification of the approved labeling
- Changes in API supplier
- Changes where the submission of an investigational new drug application (IND) is needed[40]

There are circumstances in which it may be possible to design and submit a CP for these types of CMC changes, but a reporting category other than prior approval supplement (PAS) for changes implemented under such a protocol would generally not be justified because the complexities or uncertainties associated with the change result in too high or uncertain risk to the product quality for that specific product. In these cases, a CP may still be useful to gain agreement with the agency on the data required to support a change(s), but otherwise, we recommend the use of a standard approach (e.g., submission of a supplement with commercial-scale manufacturing data before approval).

2. Can I submit multiple CPs to my application?

Yes. You can submit one or more CPs to address post-approval CMC change(s) within your original application. If submitting more than one CP for a marketed product, one PAS should be submitted for each CP. For a marketed product, if more than one CP is needed to address multiple related changes (e.g., a site change that involves equipment and/or manufacturing changes; a formulation change that involves a specification change), we recommend that these be submitted in the same

[40] See 21 CFR part 312.

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PAS. However, if you are submitting more than one CP for unrelated changes to a marketed product, one PAS should be submitted for each CP.

Where there is a possibility that the changes outlined in 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 implementation of the change(s). In some cases, it can be useful to discuss the specific situation with the appropriate FDA review division before submitting.

3. Can I submit multiple changes under a single CP?

Multiple, related changes that are to be implemented simultaneously can be submitted in a single CP. However, such changes can result in combined effects that may not be anticipated when considering the individual changes alone. You should address the risk of adverse effects as a result of such multiple changes in the supporting information for the CP.

4. How can I assess the effect of a CMC change on the product under a CP?

You should assess the effect of a CMC change on product quality under a CP by employing: (1) an understanding of the product and the manufacturing process, (2) a robust control strategy, (3) risk management activities over a product's life cycle, and (4) an effective pharmaceutical quality system.[41] Under a CP, test and study results from the product manufactured before the change are compared to those of the product from commercial batches manufactured after the change. These tests and studies can include evaluation beyond standard in-process controls and testing for conformance to specifications. The criteria (including statistical methods) to be met for each test and study used in the comparison should be prospectively described. Justification of the effect of the change on the product typically includes meeting manufacturing process controls, specifications, and additional criteria established for characterization tests and studies, including impurities profiles and stability studies. Criteria also can include statistical trending or analysis of variability within specification limits.

5. Can I submit a CP for changes that can be made repeatedly over the life cycle of the product?

A CP can be designed to be used repeatedly to make a specified 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 multiple changes over time in the supporting information for the CP. You should build sufficient safeguards into the change process described in the CP to ensure that the effects of the changes will not result in an adverse effect on product quality over time. Also, you should reevaluate the CP before each usage to ensure that it remains scientifically sound over time.[42] A notification

[41] See ICH guidances for industry on *Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management* and *Q10 Pharmaceutical Quality System.*

[42] See Section II.

using the approved reporting category must be submitted to the application each time a change is implemented under a CP.[43]

6. Can changes that apply to multiple products be covered under a CP?

A CP can be used to provide for a CMC change that applies to multiple products marketed by the same applicant (e.g., change in the manufacture of a drug substance used in multiple products, change in a facility used for manufacture of multiple products, change in an analytical procedure, change to a container closure system used for multiple products).[44] Such CP submission should include the plan for reporting the data that is applicable to all of the affected applications (product-wide data) as well as the data that applies to each of the individual affected applications (product-specific data), as applicable. While it may be possible to design a CP that applies to multiple products, most CPs will include plans to generate product-specific data. In the latter case, separate PASs will need to be submitted to the individual affected applications. For the simultaneous submission of a CP for an identical CMC change(s) that affects multiple applications (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 advice on the appropriate content and format of the submission(s).[45,46]

7. Under what circumstances will FDA not approve a comparability protocol?

FDA does not intend to approve a PAS containing a CP if, after substantive review, we find that the CP is deficient.[47] For example:

- 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 the 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 on the product quality, is not specified.

- The CP submission does not have sufficient supporting information to reasonably predict whether the proposed CMC change would have an adverse effect on product quality.

[43] See 21 CFR 314.70; 21 CFR 601.12(a)(1).
[44] See 21 CFR 314.50(g)(1).
[45] See SOPP 8422: Processing of Trans-BLA Submissions http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm252472.htm.
[46] If a CP is intended to apply to multiple ANDAs, you should submit the CP as part of each original ANDA; for marketed products, you should submit a PAS containing the CP to each affected ANDA. You can designate a lead ANDA and indicate that the same CP is intended to be applied to additional ANDAs, but the appropriate user fee will need to be paid for each affected ANDA.
[47] See 21 CFR 314.70(e) and 21 CFR 601.12(e).

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- The proposed tests, studies, and criteria are not sufficiently rigorous to ensure inconsequential change to product quality.

- The tests and studies to be performed are considered insufficient, and a nonclinical safety or clinical study would be needed, to demonstrate the lack of adverse effect of the specified type of change on product quality.

- The CP submission does not provide sufficient information to identify an appropriate reporting category for notification of the Agency of the implementation of the proposed change.

8. What is the reporting category for a change made under an approved CP?

You should propose an appropriate reduced reporting category for implementation of a change(s) at the time the CP is submitted. The CP submission should propose a reporting category commensurate with your understanding of the product, manufacturing process, and control strategy, and with the risks associated with the proposed change(s).

9. Can I submit a CP to allow changes to the manufacturing processes for multiple drugs under one life cycle CMC change management system?

A CP may be expanded to cover a broad range of manufacturing changes that are likely to occur over the life cycle of one or more products. However, each change still should be supported and planned according to the principles in this CP guidance document.

B. Formulation (Component and/or Composition) Changes

Can I make formulation (component and/or composition) changes under a CP?

Formulation changes that need clinical and/or bioequivalence studies are inappropriate for a CP.[48] However, a CP could be useful for changes in the product where a bioequivalence study would not be needed. The latter includes a proposed change where you have sufficient data from a completed study that support the proposed change (e.g., results of a bioequivalence study to determine biopharmaceutics classification).[49] Such formulation changes should be supported by relevant product development information.

[48] FDA has issued two guidances that make recommendations about when bioequivalence studies should be conducted for postapproval changes. See guidance for industry *Immediate Release Solid Oral Dosage Forms*: *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* and *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*.

[49] See guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.*

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C. Manufacturing Site Changes

Does FDA have any recommendations or issues for industry to consider regarding manufacturing site changes under a comparability protocol?

Future manufacturing site changes or certain other changes that may require a facility evaluation proposed in a CP generally do not justify a reporting category other than a PAS or CBE-30. This is because FDA will need to evaluate whether the facility impacted by the change should be subject to a preapproval inspection at the time that the site change or other change(s) is to be made. Such a facility assessment generally includes evaluation of 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 assessment cannot be effectively conducted at the time of CP submission when certain factors at the time the change is proposed to take place may be different at the time the CP is submitted, for example, when the facility cannot be specified (e.g., there are plans to expand manufacturing capacity, but the planned expansion site has not been determined) or when the change is proposed to take place well in the future. In addition, for difficult to characterize products, many site changes will require a pre-approval inspection and therefore a reporting category lower than PAS would not be justified.

If FDA determines that a preapproval inspection is needed within the 30 days after receipt of a CBE-30 submission for a site change, a PAS will be necessary to gain approval for the new site and any associated process changes. If the CBE-30 is submitted as a supplement to an NDA or BLA, the submission will be converted to a PAS. If the CBE-30 is submitted as a supplement to an ANDA, FDA will notify the applicant. The applicant may resubmit the supplement as a PAS along with any required user fee.[50]

D. Manufacturing Process Changes

1. Can a CP be used to describe a wide range of potential parameter changes to a manufacturing process?

A CP can be appropriately used to provide for a wide range of potential parameter changes to a manufacturing process using a risk-based approach, if you have a high level of process and product 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. In many cases, it may be possible to group unspecified parameter changes by individual unit operation or groups of unit operations. Often, pilot or smaller scale data can be used to identify the potential risks to product quality and help devise a suitable evaluation plan. The specific tests and studies proposed to evaluate the change should address how quality could be assured for the product, including each of the product and/or intermediate CQA.

[50] See draft guidance for industry *ANDA Submissions — Prior Approval Supplements Under GDUFA*. When final, this guidance will represent FDA's current thinking on this topic.

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The risk assessment should also consider how multiple manufacturing changes can result in combined effects that might not arise from individual 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.

2. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that risk changing the structure of the drug substance?

In general, you should include in your CP appropriate structural characterization, analytical procedures to be used, and criteria to demonstrate the lack of adverse effect on the product quality of manufacturing process changes that risk changing the structure of the drug substance. Depending on the type and complexity of the drug substance, functional characterization and additional studies should also be included.[51] For products that are difficult to characterize, we recommend that you contact the appropriate FDA review division. For example:

For chemical drug substances, you should include appropriate structural characterization, analytical procedures to be used, and criteria to unequivocally demonstrate that the chemical structure remains unchanged in a CP for a manufacturing process change that could affect the chemical structure (e.g., stereoconfiguration) 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., cell line change, change in biosynthesis/bioreactor conditions) could affect the structure (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, carbohydrate and attachment site analysis) and functional characterization (e.g., biological activity, binding assay), analytical procedures to be used, and criteria to demonstrate that the products before and after the change are analytically comparable.

3. Does FDA have any recommendations about what I should include in a CP for manufacturing process changes that risk changing 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). While not typically necessary, you may also choose to demonstrate the suitability of the drug substance for the drug product manufacturing. Regardless of the approach taken, it is important in this situation to describe and assess how the change is expected to affect clinical performance and safety of the product.

4. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that risk changing the impurity profile?

[51] See ICH Q5E guidance.

A CP should include a specific plan to determine any qualitative and quantitative changes to the impurity profile of the drug substance, product, intermediate, in-process material, or other material 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 measure and control the impurity profile. For certain synthetic and semisynthetic drug substances, you can assess the impurity profile in an isolated intermediate following the manufacturing process step where the change is made. Analytical procedures should be capable of detecting new impurities or other changes in the product that could result from the change. These procedures could be in addition to the validated regulatory methods.

For drugs derived from a biological source, this can include assessment of process removal, inactivation of 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.

5. Does FDA have other recommendations or issues for industry to consider regarding changes to manufacturing process controls under a CP?

In cases where a proposed CP provides for modified or new process controls as a result of a manufacturing change, 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. The controls for the new manufacturing process should be sufficiently described so that the assurance of product quality can be ascertained.

6. Does FDA have any recommendations or issues for industry to consider regarding a CP for manufacturing process changes that risk changing the in vivo release characteristics of the product?

You should include appropriate comparative in vitro release characterization for the products before and after the change in a CP for a manufacturing process change that could affect the in vivo release characteristics of the dose delivered to the patient.[52] You should establish the adequacy of the in vitro characterization to assess the effect of the change(s) without the need for clinical and/or bioequivalence studies.

E. Specification, Including Analytical Procedure (Methods), Changes

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

Specifications (e.g., a list of tests, analytical procedures, and appropriate acceptance criteria) are the quality standards provided in an approved application to confirm the quality of the drug substances, products, intermediates, raw materials, reagents, components, in-process materials, container closure

[52] See FDA *Scale-Up and Postapproval Changes* (SUPAC) guidances listed in footnote 47.

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systems, and other materials used in the production of the drug substance and product.[53] Changes to specifications that ensure the same or increased product quality standards when compared to the original specifications can be included in a CP.

A CP to establish a new regulatory analytical procedure or a modification of an existing analytical procedure should include justification for the change. If the procedure will replace an existing regulatory procedure provided in an approved application, then the new regulatory procedure should be scientifically sound and equivalent to or better than the currently approved one.[54] The CP also should include the specific plan and acceptance criteria for validation of the modified or new procedure. Method validation data should be submitted with the notification of the implemented change. For alternative analytical procedures, comparative data to the FDA-approved procedure should also be submitted.

F. Packaging Changes

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

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

G. Process Analytical Technology Changes

Does FDA have any recommendations regarding process analytical technology implementation or changes under 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).[55]

[53] See 21 CFR 314.3 and 600.3, and ICH guidances for industry on *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.* See also the FDA guidance for industry, *Analytical Procedures and Methods Validation for Drugs and Biologics.*

[54] See the guidance for industry on *Analytical Procedures and Methods Validation for Drugs and Biologics*.

[55] See the guidance for industry on *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.

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