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# 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### ***DRAFT GUIDANCE***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)**

**April 2016  
Pharmaceutical Quality/CMC**

**Revision 1**

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# Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry

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\*Insofar as section V of this guidance sets forth that certain modifications to an approved comparability protocol may be submitted in changes being effected supplements rather than a prior approval supplements, it will have binding effect upon finalization.

*Contains Nonbinding Recommendations\**

*Draft — Not for Implementation*

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1                   **Comparability Protocols for Human Drugs and Biologics:**  
2                   **Chemistry, Manufacturing, and Controls Information**  
3                   **Guidance for Industry<sup>1</sup>**  
4  
5

6  
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration  
8 (FDA or Agency) on this topic. With the exception of the discussion regarding submission of changes to a  
9 comparability protocol in a changes being effected supplement,<sup>2</sup> it does not establish any rights for any person  
10 and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of  
11 the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
12 for this guidance as listed on the title page.  
13

14  
15 **I. INTRODUCTION**  
16

17 This guidance provides recommendations to holders of applications for human drugs and biologics on  
18 implementing a chemistry, manufacturing, and controls (CMC) postapproval change through the use  
19 of a comparability protocol (CP). It replaces the draft guidance that published in February 2003,  
20 titled *Comparability Protocols: Chemistry, Manufacturing, and Controls Information*.  
21

22 A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC  
23 postapproval change(s) on the identity, strength, quality, purity, and potency of a drug product or a  
24 biological product (i.e., product),<sup>3</sup> as these factors may relate to the safety or effectiveness of the  
25 product (i.e., product quality).<sup>4</sup> Submission of a CP in an original application or prior approval  
26 supplement (PAS) allows the agency to review a description of one or more proposed CMC  
27 postapproval changes, supporting information including any analysis and risk assessment activities, a  
28 plan to implement the change(s), and, if appropriate, a proposed reduced reporting category for the  
29 change(s). Approval of the original application containing the CP or a subsequent PAS containing the  
30 CP can provide an applicant with an agreed-upon plan to implement the specified change(s), and in  
31 many cases, a justification to report the change(s) in a reduced reporting category, contingent upon  
32 the applicant's analysis of the data from the implementation of the change. In many cases, using a  
33 CP will facilitate the subsequent implementation and reporting of CMC changes, which could result  
34 in moving a product into distribution or facilitating a proactive approach to reinforcing the drug

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<sup>1</sup> 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).

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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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35 supply chain sooner than if a protocol were not submitted. This guidance is intended to establish a  
36 framework to promote continuous improvement in the manufacturing of quality products by  
37 encouraging applicants to employ:

- 38
- 39 • Effective use of knowledge and understanding of the product and manufacturing process
- 40
- 41 • A robust control strategy
- 42
- 43 • Risk management activities over a product's life cycle
- 44
- 45 • An effective pharmaceutical quality system
- 46

47 This guidance applies to CPs submitted to new drug applications (NDAs), abbreviated new drug  
48 applications (ANDAs), and biologics license applications (BLAs), and supplements to these  
49 applications regulated by the Center for Drug Evaluation and Research (CDER) and the Center for  
50 Biologics Evaluation and Research (CBER). The scope of this revised draft guidance does not  
51 include animal drugs.<sup>5,6</sup>

52

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

---

<sup>5</sup> 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*.

<sup>6</sup> 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.

<sup>7</sup> 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*.

<sup>8</sup> 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](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm) or the FDA Biologics guidance page at [www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

<sup>9</sup> See

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836>.

<sup>10</sup> See <http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/default.htm>.

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62 In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead,  
63 guidances describe the Agency’s current thinking on a topic and should be viewed only as  
64 recommendations, unless specific regulatory or statutory requirements are cited. The use of the word  
65 *should* in Agency guidances means that something is suggested or recommended, but not required.  
66 Insofar as section V of this guidance sets forth that certain modifications to an approved comparability  
67 protocol may be submitted in a changes being effected supplement rather than a prior approval  
68 supplement, it will have binding effect upon finalization.  
69

### **70 II. BACKGROUND**

71  
72 As an NDA, ANDA, or BLA applicant, you are responsible for validating the effects of any  
73 manufacturing change on the identity, strength, quality, purity, and potency of the drug as these  
74 factors may relate to the safety or effectiveness of the drug before distributing the product made with  
75 the change.<sup>11</sup> You must notify FDA of a change to the conditions established in an approved  
76 application in accordance with the regulatory requirements outlined in 21 CFR 314.70 and 601.12. In  
77 those regulations, these postapproval CMC changes to established conditions are categorized into one  
78 of three reporting categories depending on whether the change(s) has a substantial, moderate, or  
79 minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the  
80 drug or biological product as they may relate to the safety or effectiveness of the product.<sup>12</sup> If a  
81 change has a substantial potential to have an adverse effect on the identity, strength, quality, purity,  
82 or potency of the drug product as these factors may relate to the safety or effectiveness of the drug (a  
83 major change), an applicant must submit and receive FDA approval of a prior approval supplemental  
84 (PAS) application before the product made with the manufacturing change is distributed. If a change  
85 has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency  
86 of the drug product, as these factors may relate to the safety or effectiveness of the drug (a moderate  
87 change), an applicant must submit a supplement at least 30 days before the product is distributed (a  
88 changes being effected in 30 days (CBE-30) supplement) or, in some cases, begin distribution upon  
89 receipt by FDA of a supplement for the change (CBE-0 supplement). If a change has a minimal  
90 potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug  
91 product, as these factors may relate to the safety or effectiveness of the drug (a moderate change) (a  
92 minor change), an applicant may proceed with the change, but must notify FDA of the change in the  
93 next annual report in accordance with 21 CFR 314.81 or 21 CFR 601.12(d), as applicable.  
94

95 The regulations also provide for protocols as an optional way to manage postapproval changes.<sup>13</sup> A  
96 CP can be submitted in an original application or can be submitted as a PAS as provided for in 21  
97 CFR 314.70(e) or 601.12(e).  
98

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<sup>11</sup> 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)).

<sup>12</sup> See 21 CFR 314.70 and 21 CFR 601.12.

<sup>13</sup> See 21 CFR 314.70(e) and 21 CFR 601.12(e).

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99 Regardless of the type of change, the methods used and the facilities and controls used for the  
100 manufacture, processing, packaging, or holding of a drug must comply with current good  
101 manufacturing practices (CGMPs).<sup>14</sup> CGMPs provide for the implementation of oversight and  
102 controls over the manufacture of drugs to ensure quality, including managing the risk of and  
103 establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished  
104 products.<sup>15</sup> All manufacturing and laboratory changes must be evaluated and approved by the quality  
105 control unit.<sup>16</sup> You are responsible for evaluating, at least annually, the quality standards of each  
106 product to determine the need for changes in product specifications or manufacturing or control  
107 procedures.<sup>17</sup>

108  
109 Other FDA and ICH guidances also discuss assessing and reporting of CMC postapproval changes<sup>18</sup>  
110 and CGMP.<sup>19</sup> You should refer to them in addition to this guidance, when planning to make CMC  
111 postapproval changes.

### 112 III. OVERVIEW

113  
114  
115 A CP describes the specific tests and studies to be performed and the acceptance criteria to be  
116 achieved to demonstrate the lack of adverse effect of one or more proposed CMC changes on product  
117 quality. The description of the specific tests and studies to be performed should also include the  
118 analytical procedures to be used or reference thereto.<sup>20</sup> Analytical procedures include regulatory  
119 analytical procedures and those used for characterization studies.

120  
121 A CP may be submitted as part of an original marketing application or can be submitted after  
122 approval of the original application as a PAS (a major change). The supplement containing the CP  
123 must be approved before distribution of a drug product produced with the change(s) as outlined in the  
124 protocol (see 21 CFR 314.70(e) and 601.12(e)). A CP, once approved, can be for a one-time  
125 change(s), or be used repeatedly for a specified type of change over the life cycle of a product. A CP

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<sup>14</sup> 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.

<sup>15</sup> 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).

<sup>16</sup> For CGMP information on changes to products, see 21 CFR 211.22, 211.100, 211.110, 211.160, and 211.180.

<sup>17</sup> 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).

<sup>18</sup> 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).

<sup>19</sup> For example, see ICH Q7 and ICH Q10.

<sup>20</sup> 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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126 can also be submitted to cover an identical change(s) that affects multiple applications (grouped  
127 supplements, trans-BLA).<sup>21</sup>

128  
129 A CP can be useful in providing predictability for applicants who anticipate the need to implement  
130 future changes to an approved product, including its manufacturing process. The drivers for such  
131 changes include business needs, expanding markets, process improvements, potential for drug  
132 shortage, and accelerated manufacturing development that occur with drugs subject to expedited  
133 programs.<sup>22</sup> By delineating the specific approach to be used to evaluate one or more future changes  
134 and the rationale for that approach, the applicant can gain the Agency's approval of the plan well in  
135 advance of the need to implement the change(s). This process can facilitate a more efficient  
136 submission process for the applicant and review process for FDA. In addition, depending on the  
137 extent of available knowledge regarding the product and process, the associated risk of the proposed  
138 change(s), and the control strategy in effect, the Agency may be able to approve a protocol that  
139 justifies reporting certain changes in a manner not requiring approval from FDA prior to distribution  
140 of a product produced with the change (i.e., a CBE-type supplement or an annual report).

141  
142 We recommend that you consider a CP submission that proposes a reduced reporting category for  
143 particular changes only if you have a sufficient understanding of the product and manufacturing  
144 process to assess the risks associated with implementing the proposed change(s).

145  
146 Your understanding should be derived from one or more of the following, as appropriate:

- 147
- 148 • Prior knowledge<sup>23</sup>
  - 149
  - 150 • Development of the drug substance and its manufacturing process<sup>24</sup>
  - 151
  - 152 • Pharmaceutical development (development of the product and its manufacturing  
153 process)<sup>25</sup>
  - 154
  - 155 • Process validation activities<sup>26</sup> and commercial-scale production experience
  - 156
  - 157 • Quality risk management activities<sup>27</sup>
  - 158

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<sup>21</sup> 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.

<sup>22</sup> See the guidance for industry on Expedited Programs for Serious Conditions – Drug and Biologics

<sup>23</sup> 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.

<sup>24</sup> See the ICH guidance for industry on *Q11 Development and Manufacture of Drug Substances*.

<sup>25</sup> See the ICH guidance for industry on *Q8(R2) Pharmaceutical Development*.

<sup>26</sup> See the FDA guidance for industry on *General Principles of Process Validation*.

<sup>27</sup> 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<sup>28</sup>

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 proposed 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**

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<sup>28</sup> For example, studies performed at pilot scale or laboratory scale.

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

- 203
- 204 • A description of and rationale for the proposed change(s)
- 205
- 206 • Supporting information and analysis
- 207
- 208 • Comparability protocol for the proposed change(s)
- 209
- 210 • Proposed reduced reporting category
- 211
- 212 • Other information
- 213

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

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

218  
219 The proposed change(s) should be described in sufficient detail to enable the Agency to evaluate the  
220 relevancy and adequacy of the CP. We recommend that you include information on the basis and  
221 rationale for the change(s), where applicable.

### **C. Supporting Information and Analysis**

222  
223 Supporting information submitted with the CP should demonstrate your understanding of those  
224 aspects of the product, manufacturing process, and control strategy that are relevant to the proposed  
225 change(s).

226  
227 The supporting information should include the following, as applicable:

- 228
- 229
- 230
- 231 • Prior knowledge to justify the proposed change(s)
- 232
- 233 • A summary of the risk assessment of the proposed change(s)
- 234

235 This assessment should identify the potential effects of the change(s) on product quality.<sup>29</sup>  
236 If multiple changes are proposed for simultaneous implementation or if a specified type of  
237 change will be made repeatedly over the life cycle of the product, the risk assessment  
238 should also address the potential for cumulative effects of these changes on product  
239 quality.

240

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<sup>29</sup> 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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- 241       • Information from development of the drug substance and manufacturing process and/or  
242       pharmaceutical development that contributes to the scientific and technological  
243       understanding of a proposed change(s) and its predicted effects on product quality of the  
244       product  
245  
246       Development batches used to support the CP should be described according to batch size or  
247       scale, site and date of manufacture, route and/or process used, and intended purpose.  
248
- 249       • Any studies conducted to gain an increased understanding of the proposed change(s) and  
250       the predicted effects on product quality.  
251  
252       For example, application of statistically designed experiments and/or process analytical  
253       technology (PAT) can be used to gain such an understanding.  
254
- 255       • Supporting information relevant to well-characterized recombinant DNA-derived  
256       products.<sup>30</sup>  
257

258       The amount of supporting information that should be provided will depend on, and be commensurate  
259       with, the complexity of the product and the planned change. For any information that is already  
260       submitted in the same NDA, ANDA, or BLA, simply indicate where this information can be found  
261       (e.g., provide the volume and page number).  
262

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

263  
264  
265       The CP for the proposed change(s) should describe, in sufficient detail for FDA to assess the CP, the  
266       specific tests and studies to be performed, including analytical procedures to be used and criteria to  
267       be achieved, to demonstrate the lack of adverse effect on the product quality. These tests and studies  
268       should be performed at commercial manufacturing scale.<sup>31</sup> The CP should use a combination of both  
269       routine quality controls (e.g., specifications, process controls) and non-routine tests and studies (e.g.,  
270       characterization tests and studies, stability studies). Increased sampling for these tests and studies  
271       may be appropriate. Criteria for the expected results should be established for each of these tests and  
272       studies. The level of detail that should be provided will depend on the complexity of the change and  
273       the specific risks associated with the change to product quality.  
274

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

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<sup>30</sup> See ICH Q5E.

<sup>31</sup> Commercial-scale batches should be used for implementation, except where not feasible (e.g., viral clearance studies).

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

284  
285 Characterization tests and studies are an essential part of an assessment of the effects of the proposed  
286 change(s) on product quality. You should provide scientific justification for the design of studies,  
287 selection of the tests, and analytical procedures and ensure they are capable of providing the  
288 information needed to assess the effects of the proposed change(s) and ensure product quality.  
289 Comparison of impurities profiles before and after a change should typically be performed. Stability  
290 studies (e.g., real condition, forced degradation), may also be appropriate and should provide a direct  
291 comparison of products manufactured before and after the change to ensure that the product will  
292 maintain quality throughout its shelf life after implementation of the proposed change(s). Any other  
293 studies based on your risk assessment plan also should be included, where appropriate.

294  
295 Analytical procedures should be described in the CP or incorporated by reference to those previously  
296 submitted in your application. Information to support that the methods are appropriate for their  
297 intended purpose also should be provided. We encourage you to use analytical procedures, sampling  
298 methodologies, and appropriate statistical methods that provide a scientifically valid, statistical  
299 assessment of product quality, including product variability. Such procedures can include online  
300 determinations and statistical processing of data. Data analysis methods and their selection and  
301 development should be described, including statistical methods to be used.

302  
303 Criteria that ensure the quality of the product after implementation of the CMC change(s) should be  
304 established and provided in the CP. Relevant and clearly defined acceptance criteria to be met  
305 demonstrating that the change was successful should be specified for each characterization test and  
306 study. You also should include acceptance criteria related to the success of the change for impurity  
307 profiles, stability studies, and any other studies, where applicable. Criteria also may include  
308 statistical trending or analysis of variability within specification limits. The acceptance criteria to be  
309 used for assessment should take into account your understanding of those aspects of the product,  
310 manufacturing process, control strategy, and risks that are relevant to the proposed change(s). The  
311 intended use of the product in the clinical setting should also be taken into account. The acceptance  
312 criteria for the change can allow for differences in product attributes if you provide justification based  
313 on your assessment of the effect(s) of the change on safety and effectiveness. If you anticipate such  
314 differences, they should be prospectively described.

### **E. Proposed Reduced Reporting Category**

315  
316  
317  
318 We recommend that you propose an appropriate reduced reporting category for implementation of  
319 each change (i.e., an annual report, CBE, or CBE-30). FDA will evaluate your proposed reporting  
320 category as part of its review of the CP submission and communicate any concerns about your  
321 proposal. FDA approval of the submission containing the CP will include your proposed reporting  
322 category, if appropriate, for each of the specified CMC changes.

323  
324 However, for certain changes, a reduced reporting category may not be justified (e.g., where data  
325 from nonclinical safety, pharmacokinetic/pharmacodynamic, and safety and efficacy studies are  
326 needed to evaluate the effect of changes on product quality; future manufacturing site changes or

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

329

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

333

### **F. Other Information**

334

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

337

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

341

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

343

344 For biological products that are not specified biological products,<sup>33</sup> you should provide the  
345 qualification studies to be completed for new or modified manufacturing equipment and facilities,  
346 and the criteria to be met.

347

### **V. MODIFICATIONS TO AN APPROVED COMPARABILITY PROTOCOL**

348

349 After submission and prior to approval of the original application or a PAS containing the CP, any  
350 proposed modification to the CP will be considered an amendment. After approval of the submission  
351 containing the CP, any modification to the CP must be submitted as a new PAS (see 314.70(e) and  
352 601.12(e)).

353

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

360

361

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

365

- 366 • Inclusion of an additional approved application in a previously approved CP which covers  
367 an identical change(s) that affects multiple applications<sup>34</sup>

368

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<sup>32</sup> See footnote 15.

<sup>33</sup> See 21 CFR 601.2(a) 1-4.

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369  
370 The following is an example of modifications to an approved CP that are considered to have a  
371 moderate potential to have an adverse effect on the product quality. If these planned modifications  
372 are included in the scope of the original CP submission, they must be submitted as a CBE  
373 supplement:

- 374  
375 • Addition of a test, study, or acceptance criterion not specified in an approved CP that  
376 provides for the same or increased level of rigor of the CP for assessing the effect of the  
377 change(s) on product quality

378  
379 Upon finalization of this draft guidance, submission of the modifications to an approved comparability  
380 protocol described above in a CBE-30 or CBE supplement rather than a prior approval supplement will be  
381 binding.

382  
383 The appropriate FDA review division can be consulted for further advice on change(s) to an approved  
384 CP for a specific product on a case-by-case basis.

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

385  
386  
387  
388  
389 When making a change(s) in accordance with the provisions of an approved CP, you should review  
390 the risk assessment provided in the initial CP submission and compare it with current knowledge to  
391 ensure that the outcomes of that risk assessment as they pertain to the planned change(s) remain  
392 valid. If the review of the initial risk assessment indicates a substantive difference in the previously  
393 described level of risk associated with making the change, either higher or lower, this may affect the  
394 reporting category for the change specified in the approved CP. In this case, we recommend that you  
395 contact the appropriate FDA review division because it may be necessary to modify the CP, the  
396 proposed reporting category, or both. In addition, you should confirm that your control strategy will  
397 continue to ensure that product will be produced consistently after implementation of the change(s).  
398 Finally, we expect that the change outlined in the approved CP will be implemented within your  
399 change management system as part of your overall pharmaceutical quality system.<sup>35</sup> You are  
400 responsible for ensuring that the facility(ies) where the change is to be made is capable of  
401 implementing the change in accordance with current good manufacturing practice (CGMP). For  
402 example, an “official action indicated” compliance status (see the FDA inspection classification  
403 database<sup>36</sup>) or issuance of an FDA warning letter to that facility can be indicative that the facility is  
404 not capable of implementing the change in accordance with CGMP. If any impacted facility is not  
405 capable of implementing the change in accordance with CGMP, the approved CP should not be  
406 implemented. If you still wish to make the change, you should follow applicable regulations and  
407 guidance, not the approved CP, to determine the appropriate reporting category for the change.  
408

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<sup>34</sup> See footnote 19.

<sup>35</sup> 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.

<sup>36</sup> Available at <http://www.accessdata.fda.gov/scripts/inspsearch/>.

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

412  
413 After a change(s) is made according to an approved CP for which the reporting category does not  
414 require prior approval, you should collect and analyze process validation and commercial-scale data  
415 to establish whether implementation of the change(s) has been successful (see section IV. D.).

416  
417 If the data collected do not meet the approved criteria in the CP or there is an otherwise unwanted or  
418 unpredicted outcome, product manufactured by the altered process must *not* be distributed.<sup>37</sup> In  
419 addition, you should include a statement in the next annual report confirming that the change(s) has  
420 not and will not be implemented under the provisions of the CP. If you wish to pursue such  
421 change(s), you should contact the appropriate FDA review division to discuss an acceptable course of  
422 action.

423  
424 Regardless of the reporting category in the approved CP, ongoing verification beyond that reported  
425 can and should be performed under your pharmaceutical quality system to continue to evaluate and  
426 ensure that there is a lack of adverse effect of the change(s) on product quality. The data associated  
427 with the implementation of the change(s) under a CP should be captured as part of your knowledge  
428 management system<sup>38</sup> to inform future product and process development; further, these data should  
429 be retained at the facility and be available for review by FDA at the Agency's discretion under  
430 CGMP.<sup>39</sup>

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

431  
432  
433  
434  
435 As required by 21 CFR 314.70, you must notify FDA about each change in each condition  
436 established in the approved application beyond the variations already provided for in the application;  
437 for these changes you must notify FDA about the change in a supplement or by inclusion of the  
438 information in the annual report as described in 314.70(b)-(d). As required by 21 CFR 601.12, you  
439 must inform the FDA about each change in the product, production process, quality controls,  
440 equipment, facilities, responsible personnel, or labeling established in the approved license  
441 application(s).

442  
443 However, with an approved CP, upon successful completion of the plan for implementation of the  
444 change(s) as described in the CP, you can report the change(s) using the approved reporting category.  
445 The level of detail of the information provided should be commensurate with the change(s) and  
446 reduced reporting category. This submission should begin with a heading that identifies the  
447 change(s) as being made under an approved CP and should include the following:  
448

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<sup>37</sup> See section 506A(b) of the FD&C Act, 21 CFR 314.70, 21 CFR 601.12.

<sup>38</sup> See ICH guidance for industry *Q10 Pharmaceutical Quality System*.

<sup>39</sup> See section 704 of the FD&C Act and 21 CFR 211.

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- 449 • A reference to the number and date of approval for the approved original application or  
450 supplement containing the CP  
451
  - 452 • If the approved CP provided for a reporting category other than a PAS, a statement that all  
453 approved criteria for the findings were met and that the change(s) was successfully  
454 implemented under the site’s pharmaceutical quality system, which includes approval by  
455 the quality control unit  
456
  - 457 • Details regarding the implementation of the change(s), a summary and analysis of the data  
458 (e.g., tables, graphs, charts), and any changes to the risk assessment  
459
  - 460 • Specific data if indicated to be necessary in the approved CP  
461
  - 462 • Update of the risk assessment provided with the approved CP submission (if any), or  
463 statement that risk assessment has not changed  
464
- 465 As indicated above, if the updated risk assessment indicates a substantive change in the  
466 level of risk associated with the change, this may impact the previously approved  
467 reporting category. In this case, you should contact the appropriate FDA review division.  
468
- 469 • Unexpected results that may have affected the tests or studies (if any)  
470
  - 471 • A summary of deviations and investigations performed (if any)  
472
  - 473 • Evaluation of the impact of the change on product quality  
474
  - 475 • Conclusions reached after evaluation of studies conducted to support the change  
476
- 477 Any new information regarding the change(s) (e.g., stability data) that is generated after  
478 implementation should also be included in the next annual report. After a CP is approved, annual  
479 reports for each affected application should provide updates on the status of changes covered by the  
480 CP.  
481  
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484 **APPENDIX - QUESTIONS AND ANSWERS ON COMPARABILITY PROTOCOLS**

485

486 **A. General**

487

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

490

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

494

495 • Nonspecific plans for CMC changes (e.g., “to modify the manufacturing process”)

496

497 • Changes where effect on product quality cannot be determined by defined studies, tests,  
498 analytical procedures, and criteria

499

500 • Changes where data from nonclinical safety, pharmacokinetic/pharmacodynamic, and  
501 safety and efficacy studies are needed to assess the effects of the change

502

503 • Changes that require modification of the approved labeling

504

505 • Changes in API supplier

506

507 • Changes where the submission of an investigational new drug application (IND) is  
508 needed<sup>40</sup>

509

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

517

518 *2. Can I submit multiple CPs to my application?*

519

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

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<sup>40</sup> See 21 CFR part 312.

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

527  
528 Where there is a possibility that the changes outlined in multiple CPs could have an impact on each  
529 other, you should provide an assessment of the risk of such an impact. As a scientific matter,  
530 additional studies or testing may be needed to assess the combined effect of multiple changes on  
531 product quality. Where relevant, you also should indicate the sequence for implementation of the  
532 change(s). In some cases, it can be useful to discuss the specific situation with the appropriate FDA  
533 review division before submitting.

534  
535 3. *Can I submit multiple changes under a single CP?*

536  
537 Multiple, related changes that are to be implemented simultaneously can be submitted in a single CP.  
538 However, such changes can result in combined effects that may not be anticipated when considering  
539 the individual changes alone. You should address the risk of adverse effects as a result of such  
540 multiple changes in the supporting information for the CP.

541  
542 4. *How can I assess the effect of a CMC change on the product under a CP?*

543  
544 You should assess the effect of a CMC change on product quality under a CP by employing: (1) an  
545 understanding of the product and the manufacturing process, (2) a robust control strategy, (3) risk  
546 management activities over a product's life cycle, and (4) an effective pharmaceutical quality  
547 system.<sup>41</sup> Under a CP, test and study results from the product manufactured before the change are  
548 compared to those of the product from commercial batches manufactured after the change. These  
549 tests and studies can include evaluation beyond standard in-process controls and testing for  
550 conformance to specifications. The criteria (including statistical methods) to be met for each test and  
551 study used in the comparison should be prospectively described. Justification of the effect of the  
552 change on the product typically includes meeting manufacturing process controls, specifications, and  
553 additional criteria established for characterization tests and studies, including impurities profiles and  
554 stability studies. Criteria also can include statistical trending or analysis of variability within  
555 specification limits.

556  
557 5. *Can I submit a CP for changes that can be made repeatedly over the life cycle of the product?*

558  
559 A CP can be designed to be used repeatedly to make a specified type of CMC change over the life  
560 cycle of a product. You should address the risk of adverse effects on product quality as a result of  
561 such multiple changes over time in the supporting information for the CP. You should build  
562 sufficient safeguards into the change process described in the CP to ensure that the effects of the  
563 changes will not result in an adverse effect on product quality over time. Also, you should reevaluate  
564 the CP before each usage to ensure that it remains scientifically sound over time.<sup>42</sup> A notification

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<sup>41</sup> See ICH guidances for industry on *Q8(R2) Pharmaceutical Development*, *Q9 Quality Risk Management* and *Q10 Pharmaceutical Quality System*.

<sup>42</sup> See Section II.

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565 using the approved reporting category must be submitted to the application each time a change is  
566 implemented under a CP.<sup>43</sup>

567

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

569

570 A CP can be used to provide for a CMC change that applies to multiple products marketed by the  
571 same applicant (e.g., change in the manufacture of a drug substance used in multiple products, change  
572 in a facility used for manufacture of multiple products, change in an analytical procedure, change to a  
573 container closure system used for multiple products).<sup>44</sup> Such CP submission should include the plan  
574 for reporting the data that is applicable to all of the affected applications (product-wide data) as well  
575 as the data that applies to each of the individual affected applications (product-specific data), as  
576 applicable. While it may be possible to design a CP that applies to multiple products, most CPs will  
577 include plans to generate product-specific data. In the latter case, separate PASs will need to be  
578 submitted to the individual affected applications. For the simultaneous submission of a CP for an  
579 identical CMC change(s) that affects multiple applications (e.g., grouped supplements, trans-BLA),  
580 we recommend that you contact the FDA review division for your lead (primary) application in the  
581 group of affected applications for advice on the appropriate content and format of the  
582 submission(s).<sup>45,46</sup>

583

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

585

586 FDA does not intend to approve a PAS containing a CP if, after substantive review, we find that the  
587 CP is deficient.<sup>47</sup> For example:

588

- 589 • The type of change is not specified in sufficient detail to permit identification of the tests  
590 and studies to be performed, including analytical procedures to be used, and acceptance  
591 criteria to be achieved to demonstrate the lack of adverse effect of the change on the  
592 product quality.
- 593
- 594 • Each of the tests and studies to be performed, including analytical procedures to be used  
595 and acceptance criteria to be achieved to demonstrate the lack of adverse effect of the  
596 change on the product quality, is not specified.
- 597
- 598 • The CP submission does not have sufficient supporting information to reasonably predict  
599 whether the proposed CMC change would have an adverse effect on product quality.

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<sup>43</sup> See 21 CFR 314.70; 21 CFR 601.12(a)(1).

<sup>44</sup> See 21 CFR 314.50(g)(1).

<sup>45</sup> See SOPP 8422: Processing of Trans-BLA Submissions

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm252472.htm>.

<sup>46</sup> 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.

<sup>47</sup> 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.<sup>48</sup> 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).<sup>49</sup> Such formulation changes should be supported by relevant product development information.

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<sup>48</sup> 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*.

<sup>49</sup> 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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637 **C. Manufacturing Site Changes**

638

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

641

642 Future manufacturing site changes or certain other changes that may require a facility evaluation  
643 proposed in a CP generally do not justify a reporting category other than a PAS or CBE-30. This is  
644 because FDA will need to evaluate whether the facility impacted by the change should be subject to a  
645 preapproval inspection at the time that the site change or other change(s) is to be made. Such a  
646 facility assessment generally includes evaluation of factors such as the facility's prior inspection  
647 history, prior manufacturing experience with the dosage form that is the subject of the change, and  
648 the effectiveness of the facility's pharmaceutical quality system. This type of assessment cannot be  
649 effectively conducted at the time of CP submission when certain factors at the time the change is  
650 proposed to take place may be different at the time the CP is submitted, for example, when the  
651 facility cannot be specified (e.g., there are plans to expand manufacturing capacity, but the planned  
652 expansion site has not been determined) or when the change is proposed to take place well in the  
653 future. In addition, for difficult to characterize products, many site changes will require a pre-  
654 approval inspection and therefore a reporting category lower than PAS would not be justified.

655

656 If FDA determines that a preapproval inspection is needed within the 30 days after receipt of a CBE-  
657 30 submission for a site change, a PAS will be necessary to gain approval for the new site and any  
658 associated process changes. If the CBE-30 is submitted as a supplement to an NDA or BLA, the  
659 submission will be converted to a PAS. If the CBE-30 is submitted as a supplement to an ANDA,  
660 FDA will notify the applicant. The applicant may resubmit the supplement as a PAS along with any  
661 required user fee.<sup>50</sup>

662

663 **D. Manufacturing Process Changes**

664

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

667

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

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<sup>50</sup> 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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678 The risk assessment should also consider how multiple manufacturing changes can result in  
679 combined effects that might not arise from individual changes. The risk of adverse effects as a result  
680 of such multiple changes should be addressed during manufacturing process development and  
681 included in the supporting information for the CP.

682  
683 2. *Does FDA have any recommendations or issues for industry to consider regarding a CP for*  
684 *manufacturing process changes that risk changing the structure of the drug substance?*  
685

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

692  
693 For chemical drug substances, you should include appropriate structural characterization, analytical  
694 procedures to be used, and criteria to unequivocally demonstrate that the chemical structure remains  
695 unchanged in a CP for a manufacturing process change that could affect the chemical structure (e.g.,  
696 stereoconfiguration) of the drug substance (e.g., change in route of synthesis or manufacturing  
697 process).

698  
699 For recombinant DNA-derived protein products, certain manufacturing process changes (e.g., cell  
700 line change, change in biosynthesis/bioreactor conditions) could affect the structure (e.g., amino acid  
701 substitution, post-translational modifications) of the drug substance. Therefore, you should include  
702 appropriate comparative structural (e.g. primary and higher order structure, carbohydrate and  
703 attachment site analysis) and functional characterization (e.g., biological activity, binding assay),  
704 analytical procedures to be used, and criteria to demonstrate that the products before and after the  
705 change are analytically comparable.

706  
707 3. *Does FDA have any recommendations about what I should include in a CP for manufacturing*  
708 *process changes that risk changing the physical properties of the drug substance?*  
709

710 You should include a comparison of the properties of the drug substance before and after the change  
711 in a CP for a manufacturing process change that could affect the physical properties of the drug  
712 substance (e.g., morphic forms, particle size). While not typically necessary, you may also choose to  
713 demonstrate the suitability of the drug substance for the drug product manufacturing. Regardless of  
714 the approach taken, it is important in this situation to describe and assess how the change is expected  
715 to affect clinical performance and safety of the product.

716  
717 4. *Does FDA have any recommendations or issues for industry to consider regarding a CP for*  
718 *manufacturing process changes that risk changing the impurity profile?*  
719

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<sup>51</sup>See ICH Q5E guidance.

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720 A CP should include a specific plan to determine any qualitative and quantitative changes to the  
721 impurity profile of the drug substance, product, intermediate, in-process material, or other material  
722 manufactured using the new process. You should demonstrate an understanding of the origin and  
723 risk of any new or increased level of impurities or contaminants. The CP should specify the step(s) in  
724 the manufacturing process where you measure and control the impurity profile. For certain synthetic  
725 and semisynthetic drug substances, you can assess the impurity profile in an isolated intermediate  
726 following the manufacturing process step where the change is made. Analytical procedures should be  
727 capable of detecting new impurities or other changes in the product that could result from the change.  
728 These procedures could be in addition to the validated regulatory methods.

729  
730 For drugs derived from a biological source, this can include assessment of process removal,  
731 inactivation of virus and/or other adventitious agents, viral and adventitious agents screening, and  
732 assessment of potentially immunogenic impurities (e.g., host cell proteins, aggregates), as applicable.

733  
734 5. *Does FDA have other recommendations or issues for industry to consider regarding changes*  
735 *to manufacturing process controls under a CP?*

736  
737 In cases where a proposed CP provides for modified or new process controls as a result of a  
738 manufacturing change, such modified or new controls should be suitable for their intended purpose  
739 and provide the same or increased control, when compared to the current process. The controls for  
740 the new manufacturing process should be sufficiently described so that the assurance of product  
741 quality can be ascertained.

742  
743 6. *Does FDA have any recommendations or issues for industry to consider regarding a CP for*  
744 *manufacturing process changes that risk changing the in vivo release characteristics of the*  
745 *product?*

746  
747 You should include appropriate comparative in vitro release characterization for the products before  
748 and after the change in a CP for a manufacturing process change that could affect the in vivo release  
749 characteristics of the dose delivered to the patient.<sup>52</sup> You should establish the adequacy of the in  
750 vitro characterization to assess the effect of the change(s) without the need for clinical and/or  
751 bioequivalence studies.

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

752  
753  
754  
755 *Does FDA have any recommendations or issues for industry to consider regarding*  
756 *specification changes in a CP?*

757  
758 Specifications (e.g., a list of tests, analytical procedures, and appropriate acceptance criteria) are the  
759 quality standards provided in an approved application to confirm the quality of the drug substances,  
760 products, intermediates, raw materials, reagents, components, in-process materials, container closure

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<sup>52</sup> See FDA *Scale-Up and Postapproval Changes (SUPAC)* guidances listed in footnote 47.

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761 systems, and other materials used in the production of the drug substance and product.<sup>53</sup> Changes to  
762 specifications that ensure the same or increased product quality standards when compared to the  
763 original specifications can be included in a CP.

764  
765 A CP to establish a new regulatory analytical procedure or a modification of an existing analytical  
766 procedure should include justification for the change. If the procedure will replace an existing  
767 regulatory procedure provided in an approved application, then the new regulatory procedure should  
768 be scientifically sound and equivalent to or better than the currently approved one.<sup>54</sup> The CP also  
769 should include the specific plan and acceptance criteria for validation of the modified or new  
770 procedure. Method validation data should be submitted with the notification of the implemented  
771 change. For alternative analytical procedures, comparative data to the FDA-approved procedure  
772 should also be submitted.

773

### **F. Packaging Changes**

774

775  
776 *Does FDA have any recommendations or issues for industry to consider regarding packaging*  
777 *changes under a CP?*

778

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

783

### **G. Process Analytical Technology Changes**

784

785  
786 *Does FDA have any recommendations regarding process analytical technology*  
787 *implementation or changes under a CP?*

788

789 You can propose the implementation of process analytical technology (PAT) or propose a change in  
790 PAT in a CP. Information on the suitability of a PAT tool on experimental and/or production equipment  
791 and processes can be submitted to support a CP for PAT implementation or change(s).<sup>55</sup>

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<sup>53</sup> 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*.

<sup>54</sup> See the guidance for industry on *Analytical Procedures and Methods Validation for Drugs and Biologics*.

<sup>55</sup> See the guidance for industry on *PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.