

Guidance for Industry

Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Veterinary Medicine
September 2003**

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Guidance for Industry

Comparability Protocols Protein Drug Products and Biological Products - - Chemistry, Manufacturing, and Controls Information

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Guidance for Industry¹

**Comparability Protocols-
Protein Drug Products and Biological Products –
Chemistry, Manufacturing, and Controls Information**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternate approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this document.

I. INTRODUCTION

This guidance provides recommendations to you, the applicant, on preparing and using comparability protocols for changes in chemistry, manufacturing, and controls (CMC) of products² in approved marketing applications. A comparability protocol is a comprehensive plan that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product, as they may relate to the safety or effectiveness of the product. FDA's review of the comparability protocol will include a determination of whether changes made in accordance with that protocol may be submitted under a reduced reporting category for the change because the use of the protocol reduces the potential risk of an adverse effect.

This guidance applies to comparability protocols that you would submit in biologics license applications (BLA), or supplements to BLA applications, for therapeutic recombinant DNA derived protein products, naturally derived protein products, plasma derivatives, vaccines, allergenics and therapeutic DNA plasmids. This guidance also applies to new drug applications (NDAs), abbreviated new drug applications (ANDAs),³ new animal drug applications (NADAs), abbreviated new animal drug

¹ This guidance has been prepared by the Comparability Protocol Working Group, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Veterinary Medicine (CVM) at FDA.

² The general term *product* as used in this guidance means drug substance, drug product, and intermediate, or in-process material, as appropriate.

³ Section 505 of the Federal Food, Drug, and Cosmetic Act describes three types of new drug applications: (1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1)); (2) an

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32 applications (ANADAs), or supplements to these applications for protein drug products, and not
33 sufficiently characterizable peptide products (e.g., complex mixture of small peptides).⁴

34 This guidance does not pertain to comparability protocols for human blood and blood components
35 intended for transfusion and for further manufacture,⁵ somatic cell therapy, or gene therapy vectors
36 (except therapeutic DNA plasmids). This guidance also does not pertain to vaccines for veterinary use,
37 which are regulated by United States Department of Agriculture.

38
39 FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities.
40 Instead, guidances describe the agency's current thinking on a topic and should be viewed only as
41 recommendations, unless specific regulatory or statutory requirements are cited. The use of the word
42 *should* in agency guidances means that something is suggested or recommended, but not required.

43

44 **II. BACKGROUND**

45

46 You are responsible for assessing, prior to distribution of a product, the effect of any postapproval
47 CMC changes on the identity, strength, quality, purity, and potency of the product as they may relate to
48 the safety or efficacy of the product). Such an assessment often includes data that demonstrate that the
49 pre- and post-change products (i.e., the products manufactured prior to and subsequent to a
50 manufacturing change) are comparable. You must report postapproval CMC changes to FDA, us, in
51 one of the reporting categories described by FDA (section 506A(b) of the Federal Food, Drug, and
52 Cosmetic Act (the act) (21 USC 356a).⁶ (See II.E for references). As part of its review and approval
53 of a comparability protocol to evaluate the effects of a change, if supported by the submission, FDA
54 may determine that a CMC change made under the comparability protocol will fall into a less restrictive
55 reporting category. In many cases, using a comparability protocol will facilitate the subsequent
56 implementation and reporting of CMC changes, which could result in moving a product into distribution
57 sooner than if a protocol were not submitted.

58

application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and (3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j)).

⁴ When finalized, guidance on comparability protocols that can be submitted in NDAs, ANDAs, NADA, and ANADAs for many products outside the scope of this guidance will be provided in “Guidance For Industry: Comparability Protocols -Chemistry, Manufacturing, and Controls Documentation.” FDA published a draft version of this guidance on February 25, 2003 (68 FR 8772).

⁵ Guidance on comparability protocols for human blood and blood products can be found in “Guidance For Industry: Changes to an Approved Application: Biologics Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001.”

⁶ See also 21 CFR 601.12.

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- Annual Report (AR)

This annual submission to the approved application reports changes that have minimal potential to adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

- Change-Being-Effectuated Supplement (CBE)

This submission to an approved application reports changes have moderate potential to adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. A CBE supplement would be received by FDA before, or concurrently with, distribution of the product made using the change. It is distinguishable from a Change-Being-Effectuated-in-30-Days Supplement (discussed below) because FDA has determined that, based on experience with a particular type of change, the supplement for such change is usually complete and provides the proper information, and based on assurances that the proposed change has been appropriately submitted, the product made using the change may be distributed immediately upon receipt of the supplement by FDA.

- Change-Being-Effectuated-in-30-Days Supplement (CBE-30).

This submission to an approved application reports changes that have moderate potential to adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. A CBE-30 supplement would be received by FDA at least 30 days before you may distribute the product made using the change (21 CFR 601.12(c)(3)).

- Prior Approval Supplement (PAS)

This submission to an approved application reports changes that have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. FDA would receive and approve a PAS before you may distribute the product made using the change (21 CFR 601.12(b)).

This guidance describes the general principles and procedures associated with developing and submitting a comparability protocol to us. This guidance also describes the basic elements of a comparability protocol and specific issues to consider when developing comparability protocols for changes in:

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- the manufacturing process,
 - analytical procedures,⁷
 - manufacturing equipment,
 - manufacturing facilities,
 - container closure systems, and
 - process analytical technology (PAT).

103 This guidance also discusses submitting comparability protocols in master files.

104
105 **A. What is a Comparability Protocol?**

106
107 A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific
108 CMC changes on the identity, strength, quality, purity, and potency of a specific drug product as they
109 may relate to the safety and effectiveness of the product. A comparability protocol describes the
110 changes that are covered under the protocol and specifies the tests and studies that will be performed,
111 including the analytical procedures that will be used, and acceptance criteria that will be met to
112 demonstrate that specified CMC changes do not adversely affect the product. The submission of a
113 comparability protocol is not required to make a CMC change.

114
115 **B. What is the Benefit of Using a Comparability Protocol?**

116
117 At the same time we approve a comparability protocol, we can designate,⁸ if appropriate, a reduced
118 reporting category for future reporting of CMC changes covered by the approved comparability
119 protocol (See section III.A). Furthermore, because a detailed plan will be provided in the
120 comparability protocol, we are less likely to request additional information to support changes made
121 under the protocol (See section IV.D for a potential exception). The use of a comparability protocol
122 could allow an applicant to implement CMC changes and place a product in distribution sooner than
123 without the use of a comparability protocol.

124
125 **C. When and Why Were Comparability Protocols Created?**

126
127 For many years, applicants have used protocols to implement certain types of CMC changes, such as to
128 extend an expiration dating period or to demonstrate the interchangeability of certain plastic containers.
129 More recently, there have been many improvements in the techniques for characterizing products,
130 production processes, process controls, and release testing. Because of these improvements and

⁷ The term *analytical procedure*, as used in this guidance, includes, biochemical, chemical, physicochemical, immunochemical, microbiological, and biological test procedures.

⁸ The term *designate*, in this context, refers to the reporting category agreed to by the applicant and FDA during the review of the submission containing the comparability protocol. See Section V.A.6.

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131 because we are able to better assess the potential effect of CMC changes on a product, protocols are
132 now being used with other types of CMC changes (e.g., manufacturing process, analytical procedure
133 changes). This expanded use of comparability protocols has been recognized in FDA regulations,⁹ and
134 we have received a number of requests for guidance from applicants interested in using comparability
135 protocols for these other types of changes. The use of comparability protocols for expanded types of
136 CMC changes has allowed some applicants to implement CMC changes sooner.

137

D. Why is A Guidance on Comparability Protocols Being Provided?

139

140 We have received a number of requests for guidance from applicants interested in using comparability
141 protocols for CMC changes. Our experience in reviewing comparability protocols for a variety of
142 CMC changes for biologics, including specified products and protein drug products, has been
143 incorporated into this guidance.

144

E. Where Can More Information on Postapproval Changes and Assessment of Comparability Be Found?

146

147
148 This guidance is not intended to supersede other FDA guidance documents, but rather to supplement
149 them with information on using comparability protocols to implement postapproval CMC changes. We
150 recommend that you consult all relevant guidances¹⁰ for information relating to postapproval changes.
151 The following guidances provide relevant information on: (1) assessing the effect of CMC changes on
152 product attributes, (2) providing documentation to support postapproval change, and (3) the
153 recommended reporting categories.

154

- 155 • *FDA Guidance Concerning Demonstration of Comparability of Human Biological*
156 *Products Including Therapeutic Biotechnology-derived Products, (April 1996)*
- 157 • *Guidance For Industry: Changes to an Approved Application For Specified*
158 *Biotechnology and Specified Synthetic Biological Products (July 1997)*
- 159 ■ *Guidance For Industry: Changes to an Approved Application For Biological Products*
160 *(May 1996)*
- 161 • *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an*
162 *Approved NDA or ANDA*¹¹ (November 1997)
- 163 • *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an Approved*
164 *NADA or ANADA (draft)*^{10, 12} (June 1999)

165

⁹ See, for example, 21 CFR 601.12(e). These regulations provided for the use of a pre-specified protocol, or a comparability protocol, that describes how to assess the effects of specific manufacturing changes.

¹⁰ Relevant guidance documents can be found on the internet at <http://www.fda.gov/cder/guidance/index.htm>, <http://www.fda.gov/cber/guidelines.htm>, or <http://www.fda.gov/cvm/guidance/published.htm>

¹¹ Guidance for naturally derived protein drug products

¹² This draft guidance is listed for completeness but is not intended for implementation until it has been finalized.

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166 **III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL**

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168 **A. How Does a Comparability Protocol Affect the Reporting of CMC Changes?**

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170 A comparability protocol *prospectively* specifies the planned CMC change, the tests and studies that
171 will be performed, analytical procedures that will be used, and acceptance criteria that will be met to
172 assess the effect of CMC changes. A well-planned protocol provides sufficient information for us to
173 determine whether the potential for an adverse effect on the product can be adequately evaluated.
174 When we review a comparability protocol, we will determine if a specified change can be reported in a
175 reporting category lower than the category for the same change implemented *without* an approved
176 comparability protocol. Typically, categories designated for reporting changes under an approved
177 comparability protocol are one category lower than normally would be the case (e.g., from PAS to
178 CBE-30, CBE to AR). In some cases, a reduction of more than one reporting category may be
179 possible (e.g., PAS to AR).

180

181 **B. When Might a Comparability Protocol Be Useful for a CMC Change?**

182

183 A comparability protocol could be useful for a variety of CMC changes, but there are some exceptions
184 (See Section III.C). In addition, a comparability protocol can describe a single CMC change or multiple
185 related changes, and can be particularly useful for changes of a repetitive nature. Because biologics and
186 protein drug products are complex and heterogeneous, knowledge of how product attributes affect the
187 safety and efficacy of the product is crucial in designing most comparability protocols. It is also
188 important that you have sufficient manufacturing and analytical experience to specify in advance the
189 tests, studies, analytical procedures, and acceptance criteria appropriate to assess the impact of the
190 change on the product. We recommend that you include information from developmental and
191 investigational studies, manufacturing experience, demonstrated process capability, out-of-specification
192 (OOS) investigations, and stability data with the particular product and process, and in some cases
193 manufacturing information with similar products or processes (e.g., for some monoclonal antibody
194 products). However, we also recognize that some CMC changes (e.g., some packaging changes)
195 would require less supportive information because they are less dependent on manufacturing experience.
196 We recommend that you submit comparability protocols only for CMC changes that you intend to
197 implement.

198 We recommend that you consider product-specific and process-specific attributes when determining
199 whether to develop a comparability protocol. Attributes can include, but are not limited to, the
200 following:

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- Complexity of the product structure,
- Ability to characterize the physicochemical, biochemical, immunological microbiological, and biological properties of the product,

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- 205 • Degree to which differences in product characteristics (e.g., product structure and
206 physical properties) can be detected,
- 207 • Degree of product heterogeneity,
- 208 • The effect of potential changes in the impurities on product safety,
- 209 • The robustness of the product (i.e., the ability of product to remain unaffected by
210 process changes), and
- 211 • Rigorousness of the manufacturing process controls (i.e., the ability of the manufacturing
212 process controls to ensure that the product remains unaffected by changes).

213
214 We recommend that you consider a comparability protocol only if you expect: (a) the product resulting
215 from the changes to meet the approved drug substance and/or drug product specifications and
216 predetermined acceptance criteria for non-routine characterization studies; (b) appropriate and sensitive
217 analytical procedures have been established and validated or qualified (i.e., for non-routine tests such as
218 characterization studies) to assess the effect of the change on the approved product; and (c) the
219 approved manufacturing process and equipment has been fully qualified and validated, when
220 appropriate.

221
222 Some specific examples submitted to us of changes to the manufacturing process where a comparability
223 protocol has been used include, but are not limited to, the following:

- 224
225 • Increase or decrease in batch size that affects equipment size,
226
- 227 • Modification of production operating parameters in fermentation (e.g., time,
228 temperature, pH, dO₂ (dissolved oxygen)),
229
- 230 • Adding, deleting, or substituting raw materials (e.g., buffer or media components),
231
- 232 • Mode changes (usually associated with equipment changes such as tangential flow
233 filtration to centrifugation),
234
- 235 • Establishing a new working cell bank using a modified procedure,
236
- 237 • Reprocessing the drug substance or drug product, as appropriate,
238
- 239 • Addition, deletion, or rearrangement of production steps; and
240
- 241 • Facility-related changes for products with facility/establishment information provided in
242 a BLA, or postapproval supplement to a BLA (see examples provided in Section V.
243 E.).

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C. When Might a Comparability Protocol Be Inappropriate?

A comparability protocol would be inappropriate for some CMC changes. In some cases, it may be impossible for the changes and/or plan for evaluating the effect of the CMC changes on the product to be fully described in advance. For example, a change may also be too complex to evaluate its effect on the product without efficacy, safety (clinical or nonclinical), or pharmacodynamic or pharmacokinetic (PK/PD) information.

In general, we do not recommend comparability protocols for:

- Nonspecific plans for CMC changes,
- A CMC change for which the adverse effect on the product cannot be definitively evaluated by prespecified tests, studies, analytical procedures, and acceptance criteria,
- Any CMC change that warrants the submission of an investigational new drug (IND),¹³ investigational new animal drug (INAD), or new original application, and
- A CMC change that requires efficacy, safety (clinical or nonclinical), or PK/PD data to evaluate the effect of the change (e.g., certain formulation changes, clinical or nonclinical studies to qualify new impurities, assess impurities or assess immunogenicity/antigenicity).

It may be possible to design a comparability protocol for certain CMC changes, but we may be limited in our ability to designate a reporting category other than PAS for changes implemented under such a protocol. Moreover, in some situations, these changes could require the submission of an IND, INAD, or new application. Examples of such changes can include:

- A change in the drug substance or drug product specifications (for exceptions, See Sections V.A.4 and V.C),
- A change in the qualitative or quantitative formulation of the drug product,¹⁴
- A change in the type of delivery system.
- A change in or move to a manufacturing site, facility, or area when a prior approval supplement is recommended because an inspection (e.g., current good manufacturing

¹³ INDs may be warranted in certain circumstances, such as for a change from plant, animal, or multicellular (e.g., algae, macroscopic fungi) source material to a different one (e.g., different plant species, different tissue and/or plant part, plant to animal), a change in the species of a microorganism or cell line used as source, a change in the microorganism or cell line used as source from non-recombinant to recombinant-DNA-modified, a change from a non-transgenic source to a transgenic plant or animal, or a change from one plant or animal transgenic source material to another.

¹⁴ A comparability protocol might be useful in certain cases for quantitative changes in excipients, and FDA might designate a reduced reporting category for certain types of products and changes if you have sufficient information to assess the potential effect of the change.

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274 practice (cGMP) inspection) is warranted (e.g., see examples in guidances listed in Section
275 I.D.), and

276 • Facility-related changes for products with facility/establishment information provided in a
277 BLA or postapproval supplement to a BLA. See examples provided in Section V.E.

278

279 **IV. PROCEDURES FOR COMPARABILITY PROTOCOLS**

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281 **A. How Should a Comparability Protocol Be Submitted?**

282

283 You can submit a comparability protocol in a prior approval supplement or as part of the original
284 application. However, we recommend that you evaluate the appropriateness of including the
285 comparability protocol in the original application when your experience manufacturing the product is
286 limited and it may be difficult to identify the elements of an appropriate comparability protocol (see
287 considerations in Section III.B.). We recommend that you indicate that you are submitting a
288 comparability protocol.

289

290 You may submit the proposed comparability protocol in:

291

292 • A prior approval supplement that consists only of the proposed comparability protocol.
293 You may want us to review and approve the protocol and determine the reporting category
294 for changes, evaluated under the protocol, prior to generating data specified in the protocol.

295 • A prior approval supplement that includes the proposed comparability protocol, study
296 results, and any other pertinent information as specified in the proposed comparability
297 protocol. Note that the comparability data submitted would be evaluated as part of the
298 prior approval supplement. The product already manufactured with the change can be
299 distributed only after approval of the supplement.

300 • A part of an original market application. You may want the comparability protocol
301 reviewed and approved and the reporting category determined, prior to generating data
302 specified in the protocol.

303

304 In all cases, the comparability protocol must be approved prior to distributing the product made using
305 the CMC changes specified in the protocol. As specified in your protocol, you must also complete the
306 studies that assess the effect of the changes on the identity, strength, quality, purity, and potency of the
307 product and report the results to us in accordance with the reporting category we designated as part of
308 our approval of the protocol, prior to distributing the product made with the change (Section 506A(b)
309 of the act, and 21 CFR 601.12).

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B. How are Changes and Study Results Submitted After a Comparability Protocol is Approved?

After a protocol is approved, we recommend that you document and submit each implemented change within the scope of the protocol using the reporting category that we designated. Include (1) the results of all tests and studies specified in your comparability protocol; (2) discussions of significant deviations that occurred during the tests or studies and that may have affected the tests or studies; (3) a summary of investigations performed, with analysis of the circumstances, product impact, corrective actions, and conclusions reached; and (4) any other pertinent information. We recommend that you indicate in the submission that it includes data from a change covered under a comparability protocol and provide a reference to the submission in which the comparability protocol was approved.

C. What If Study Results Do Not Meet the Criteria Specified in the Approved Comparability Protocol?

In certain instances, the changes, the tests, and/or the studies specified in an approved comparability protocol can lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance criteria). If this occurs, you can elect not to implement the change. If you decide to pursue the change, we recommend that you submit a prior approval supplement that provides the supporting data to justify why the change will not adversely affect the identity, strength, quality, purity, and potency of the specific drug product as they may relate to the safety and effectiveness of the product.

D. When Does a Comparability Protocol Become Obsolete?

New regulatory requirements, identification of a safety issue (e.g., screening for new infectious agents in materials from a biological source), identification of a new scientific issue, or technological advancement after the comparability protocol has been approved can render a protocol obsolete. We recommend that you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure that they remain current and consistent with the approved application and current regulatory and scientific standards. We recommend that you determine whether the tests, studies, analytical procedures, and acceptance criteria described in your comparability protocol are still appropriate prior to implementing and submitting a change under the protocol. We may determine that a reporting category made in the approval of a comparability protocol that becomes obsolete is no longer applicable. We may also request additional information to support a change that is evaluated using an obsolete protocol. If you find the comparability protocol is no longer correct or adequate, you should modify or withdraw the current protocol.

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348 **E. How is an Approved Comparability Protocol Modified?**

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350 You can submit a revised protocol at any time. Like an original protocol, you can submit a revised
351 protocol as a PAS to your application following the recommended submission procedures summarized
352 in Section IV.A. We recommend that you indicate in the submission that it includes a revision to an
353 approved comparability protocol and identify all modifications.

354
355 A comparability protocol should also be modified to reflect relevant changes in the application. For
356 example, you may ask FDA to approve a change in an analytical procedure that is used for release
357 testing. The new analytical procedure should also be incorporated into approved comparability
358 protocols, if appropriate. As part of the request to make the change in release testing, we recommend
359 that you clearly indicate in your submission all comparability protocols that will also be affected. The
360 specified comparability protocols would be updated as part of the submission for the change in release
361 testing, using the reporting category appropriate for that change. There would be no need to make a
362 separate submission requesting a modification of each comparability protocol. However, you should
363 wait to implement the modified comparability protocol until you are authorized to implement the change
364 in release testing.

365
366 **V. CONTENT OF A COMPARABILITY PROTOCOL¹⁵**

367
368 We recommend that that you develop and use a comparability protocol within the context of existing
369 change control procedures. Such procedures ensure that specified changes do not adversely affect the
370 identity, strength, quality, purity, or potency of the product.

371
372 In the comparability protocol, you can describe a single CMC change or multiple changes. We
373 recommend that you specify each change and define the acceptance criteria for evaluating the effect of
374 the changes. If multiple changes are included in a protocol, we recommend that the multiple changes be
375 interrelated (i.e., one change cannot be made without the others; changes focus on a common goal such
376 as production optimization). For example, a change in a fermentation medium component used to
377 produce a protein results in more rapid cell growth that in turn, causes a higher production rate of the
378 protein. Changes related to this change in culture medium could include modification in the length of cell
379 fermentation, increase in harvesting time, and/or changes to purification columns. We recommend that
380 you submit separate comparability protocols for unrelated changes.

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¹⁵ For brevity, the text focuses on comparability protocols submitted in postapproval supplements, although the option is available to include a comparability protocol in an original submission.

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382 **A. What are the Basic Elements of a Comparability Protocol?**

383

384 1. Description of the Planned Changes

385

386 A comparability protocol should provide a detailed description of the proposed changes clearly
387 identifying all differences from the conditions approved in the application. A table, diagram, and/or flow
388 chart can be included to help illustrate the differences.

389

390 2. Specific Tests and Studies to Be Performed

391

392 We recommend that you include a list of the specific tests (e.g., release, in-process) and studies (e.g.,
393 characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or
394 inactivation, validation, process development) that you will perform to assess the effect of the change on
395 the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or
396 component (e.g., container closure system) directly affected by the change. We recommend that you
397 include the rationale for selecting the particular battery of tests and studies. This rationale could include
398 a discussion of the type and extent of the change, potential effect of the change, experience with the
399 manufacturing process, and product robustness. For example, the inclusion of additional tests to check
400 for new impurities, glycosylated species or other postranslation modifications that may be formed as a
401 result of the change, or use of nonroutine studies (e.g., characterization) may be warranted. Such
402 additional testing is especially important in cases where in-process or release specifications are not
403 sufficiently discriminatory to evaluate the change, (e.g., tests for secondary or tertiary structure).

404 We recommend that you include a plan, within the protocol, to compare results from routine batch
405 release testing and, as appropriate, nonroutine testing (e.g., characterization studies) on pre- and
406 postchange products or other material, if appropriate. We recommend that you specify the number and
407 type (e.g., pilot, production) of pre- and postchange batches and/or samples that will be compared.
408 The number and type of batches and/or samples to be compared can vary depending on the extent of
409 the proposed change, type of product or process, and available manufacturing information. You can
410 use retained samples of prechange material for comparison, provided there is no significant change in
411 material during storage (e.g., level of degradants increasing over time). If you plan to use retained
412 samples, we recommend that you specify their maximum age and provide a justification with supporting
413 data for using retained samples. In general, the results from postchange material should fall within the
414 normal batch-to-batch variation observed for prechange material.

415

416 In a comparability protocol we recommend that you include a plan for the stability studies that will be
417 performed to demonstrate the comparability of the pre- and postchange product. The comparability
418 protocol should provide: (1) information that is typically provided in a stability protocol, such as the
419 number and type of batches that will be studied, test conditions, and test time points, or (2) a reference
420 to the currently approved stability protocol. You should specify the amount of stability data that will be
421 collected before the product made with the change is distributed. The plan for evaluating stability could
422 vary depending on the extent of the proposed change, type of product, and available manufacturing

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423 information. In some cases, no stability studies may be warranted or a commitment to report results,
424 when available (e.g., annual report), from stability studies postapproval can be sufficient. If you don't
425 plan to conduct stability studies, we recommend that you state this clearly and provide justification for
426 not doing so.

427
428 We recommend that you describe the differences, if any, in the tests and studies from those previously
429 reported in the approved application or subsequent updates (i.e., supplements, annual reports). We
430 recommend that you include a citation of the location in your application of any referenced tests or
431 studies.

432 433 3. Analytical Procedures to Be Used

434
435 In a protocol we recommend that you specify the analytical procedures that you intend to use to assess
436 the effect of the CMC changes on the product or intermediate material. We recommend that you use
437 analytical procedures capable of detecting and quantifying impurities (e.g., process-related impurities
438 such as host cell proteins, product-related impurities, etc.) or other effects on the product that can result
439 from the change.

440
441 Because the currently approved analytical procedures are optimized for the approved product and
442 process, you may want to use modified or new analytical procedures (for example, to monitor the
443 removal of a new process impurity generated by a new manufacturing process). In this situation, we
444 recommend that you submit results for pre- and postchange products using both the old and new
445 analytical procedures. Studies that you perform to assess the feasibility of the proposed change can
446 often be helpful in determining whether the current approved analytical procedures will be appropriate
447 for assessing the effect of the change on the product (see Section V.A.5). As appropriate, you should
448 validate new or modified analytical procedures (with establishment of corresponding acceptance
449 criteria) or revalidate existing analytical procedures. Alternatively, the plan for validation of a new
450 analytical procedure or re-validation of an existing procedure can be included within the protocol and
451 the validation report provided to the Agency in accordance with the designated reporting category (see
452 Section V.C.).

453
454 In some instances, analytical procedures are used in the characterization and/or assessment of the
455 functionality of a product, but not for batch release or for process control (e.g., NMR spectroscopy,
456 carbohydrate structural analysis, attachment site determination). If you specify these analytical
457 procedures in a comparability protocol, we recommend that you provide any replacement or
458 modification to those procedures submitted in the approved application and, as appropriate, report to
459 us results from qualification studies when a postapproval CMC change is implemented using the
460 approved comparability protocol.

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462 In cases where changes in analytical procedures are intended to be implemented independent of other
463 CMC changes, we recommend that you submit a comparability protocol specific for analytical
464 procedure changes (see Section V.C.).

465

466 4. Acceptance Criteria

467

468 We recommend that you include the acceptance criteria (numerical limits, ranges or other criteria) or
469 other acceptable results for each test and study in the protocol that will be used to assess the effect of
470 the CMC change on the product or other material and assess comparability between pre- and
471 postchange material. In general, the drug substance and drug product specifications would be identical
472 to or tighter than those in the approved application, unless otherwise justified. We recommend that you
473 identify any statistical analyses that will be performed and the associated evaluation criteria.

474

475 After implementing a change under a comparability protocol, you may find that the CMC change calls
476 for a revision of the drug product or drug substance specification. Change to that specification under
477 these circumstances would not fall under the determination of reporting category made for the
478 comparability protocol submission. Accordingly, in making your CMC change submission, we
479 recommend that you consider the recommended reporting category¹⁶ for the type of specification
480 change as well as the designated reporting category for reporting a change using your comparability
481 protocol. When the recommended reporting category for the specification change is higher (e.g., PAS)
482 than the reporting category for changes made under the comparability protocol (e.g., CBE-30), we
483 recommend that you use the reporting category associated with the specification change, that is, the
484 higher reporting category. If the recommended reporting category for the specification change is the
485 same or lower than the designated reporting category for changes made under the comparability
486 protocol, the specification can be updated and provided when you report a postapproval CMC change
487 implemented using the approved comparability protocol.

488

489 5. Data to Be Reported Under or Included With the Comparability Protocol

490

491 We recommend that you identify the type (e.g., release, long-term, accelerated and/or stress stability
492 data, as appropriate) and amount of data (e.g., 3-month accelerated, 6-month real-time stability data)
493 that you will submit at the time you report to us a postapproval CMC change implemented using the
494 approved comparability protocol and, when appropriate, generated prior to your distributing the
495 product made with the change (e.g., when proposed reporting category is a CBE-30, CBE-0, or AR).

496

497 If available, you can include any data from studies performed to assess the feasibility of the proposed
498 change with the proposed comparability protocol. Data obtained from a small-scale process or other
499 studies incorporating the proposed change can provide preliminary evidence that the change is feasible,

¹⁶ The recommended reporting categories for specification changes may be found in the guidance on *Changes to an Approved Application For Specified Biotechnology and Specified Synthetic Products and Changes To An Approved Application For Biologics*.

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500 as well as preliminary information on the effect of the change on the product. Development or feasibility
501 studies can provide insight into the relevance and adequacy of the choice of the battery of tests you have
502 identified to assess the product and/or process.

503

504 6. Proposed Reporting Category

505

506 The use of an approved comparability protocol may support a reduction in the reporting category for
507 the particular CMC change when implemented (see Section III.A). We recommend that you include a
508 proposal for the reporting category that you would use for changes implemented using the approved
509 comparability protocol. We will evaluate your proposed reporting category as part of our review of the
510 comparability protocol and communicate any concerns about your proposal. A designation of the
511 reporting category for the specified CMC changes will be included as part of the approval process for
512 the comparability protocol.

513

514 7. Comparability Not Demonstrated Using the Approved Comparability Protocol

515

516 It is anticipated that some changes in the manufacturing process will result in a postchange product that
517 cannot be demonstrated to be comparable to the prechange product without more extensive
518 physicochemical, biological, pharmacological, PK/PD, efficacy, or safety testing or in a product that
519 does not meet the prespecified acceptance criteria in the protocol. We recommend that you identify in
520 the protocol the steps you will take in such circumstances (see Section III.C.).

521

522 8. Commitment

523

524 We recommend that you include a commitment in your comparability protocol to update or withdraw
525 your protocol when it becomes obsolete (see Section IV.D).

526

527 **B. Does FDA Have Specific Concerns About Changes in the Manufacturing**
528 **Process That Should Be Addressed in a Comparability Protocol?**

529

530 In addition to the general considerations provided in Section V.A, we recommend that you consider the
531 following issues related to changes in the manufacturing process, where applicable:

532

533 1. Physicochemical and Biological Characterization

534

535 A comparability protocol would include a plan to compare the physicochemical and biological
536 characterization of the product produced using the old and new processes when these characteristics
537 are potentially affected by the change and are relevant to the safety and/or efficacy of the product. For
538 recombinant DNA-derived protein products and other products when appropriate, such
539 characterization can include structural analysis (e.g., primary, secondary, tertiary, quaternary), glycoform
540 analysis, and bioassay, as appropriate.

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541

542 2. Comparison of Impurity Profiles

543

544 A comparability protocol should include a plan to determine the impurity profile of the product
545 produced using the new process. The studies should assess product-related impurities and process-
546 related impurities including, if applicable, cell substrate-derived, cell culture-derived and downstream-
547 derived impurities. We recommend that you demonstrate the absence of any new impurities or
548 contaminants, or that they are removed or inactivated by downstream processing (e.g., clearance
549 study). You should justify any changes in the impurity profile.

550

551 If during implementation of a change under an approved comparability protocol, the data indicate that
552 nonclinical or clinical qualification studies to evaluate safety for impurities are warranted, the change
553 would not be appropriate for implementation under the approved comparability protocol (see Sections
554 III.C and V.A.7).

555

556 3. Effect on Downstream Processes

557

558 We recommend that you examine the effect of the change on downstream processes. Downstream
559 processes such as purification steps can be affected by higher product yields or shifts in impurity profiles
560 when upstream processes are modified. For example, adventitious agent removal or inactivation may
561 have to be reassessed for processes involving materials or reagents derived from a biological source.
562 We recommend that you discuss in your comparability protocol how to ensure that the entire
563 manufacturing process is adequately controlled.

564

565 4. Effect on Process Controls and Controls of Intermediates and/or In-process Materials

566

567 We recommend that you identify and justify implementation of new controls or variations from approved
568 controls. We recommend that you include in the protocol a statement that controls, including those that
569 have been validated to inactivate and remove impurities or contaminants, will be revalidated for the new
570 production process, if appropriate.

571

572 **C. Does FDA Have Specific Concerns About Changes in Analytical Procedures** 573 **That Should Be Addressed in a Comparability Protocol?**

574

575 A comparability protocol for changing an analytical procedure should provide the plan for validation of
576 the changed analytical procedure and indicate whether the protocol will be used to modify the existing
577 analytical procedure (i.e. retaining the same principle), or to change from one analytical procedure to
578 another. We recommend that you design the comparability protocol to demonstrate that the proposed
579 changes in the analytical procedures improve or do not significantly change analytical procedure

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580 characteristics that are relevant to the type of analytical procedure, its validation, and intended use (e.g.,
581 accuracy, precision, specificity, detection limit, quantitation limit, linearity, range).¹⁷

582
583 Methods validation includes an assessment of the suitability of the analytical procedure. You should
584 have in your validation plan prespecified acceptance criteria for relevant validation parameters such as
585 precision, range, accuracy, specificity, detection limit, and quantitation limit. The proposed acceptance
586 criteria for these parameters should ensure that the analytical procedure is appropriate for its intended
587 use. In the validation plan you would assess whether a revised procedure is more susceptible than the
588 original procedure to matrix effects by process buffers/media, product-related contaminants, or other
589 components present in the dosage form. You should identify in the plan any statistical analyses that you
590 will perform and whether you intend to perform product testing to compare the two procedures. The
591 need and plan for providing product testing to compare the two procedures could vary depending on
592 the extent of the proposed change, type of product, and type of test (e.g., chemical, biological).
593 When you use the new revised analytical procedure for release or process control, you should not
594 delete a test or relax acceptance criteria that we approved in your application, unless and until FDA
595 informs you that the approved acceptance criteria are no longer required.

D. Does FDA Have Specific Concerns About Changes in Manufacturing Equipment That Should Be Addressed in a Comparability Protocol?

596
597
598
599
600 Comparability protocols may be useful if applicants plan to use different equipment or plan equipment
601 changes that would effectively result in different equipment. These changes are often made in
602 conjunction with changes to the manufacturing process. Different equipment can include new models,
603 changes in capacity, construction materials (e.g., glass-lined tanks to stainless steel), equipment design,
604 and/or equipment operating principles. Comparability protocols may also be useful when additional
605 duplicative process trains (such as fermentation trains) or equipment will be added to an approved
606 manufacturing facility. We recommend that you evaluate these types of change with respect to its effect
607 on the production process prior to deciding whether a comparability protocol would be appropriate.
608 We encourage you to initiate early dialogue with us to facilitate the change, as needed.

E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities That Should Be Addressed in a Comparability Protocol?

609
610
611
612
613 The utility of a comparability protocol is often limited due to the scope of the change and the need, in
614 some cases, for an inspection. For example, a move to a new facility can involve many changes (e.g.,
615 new equipment, modified manufacturing process) that are difficult to prospectively identify as part of a
616 comparability protocol because the new facility is unknown or not constructed at the time the

¹⁷ Guidance on validation of some analytical procedures can be found in the ICH guidances on *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology* or VICH guidances on *GL1 Validation of Analytical Procedures: Definition and Terminology* and *GL2 Validation of Analytical Procedures: Methodology*.

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617 comparability protocol is being considered. We recommend that you consider carefully the
618 appropriateness of a comparability protocol for a facility change, especially one that involves many other
619 changes. For biologics, which also have application requirements described in an Establishment
620 Description section, there may be additional situations when a comparability protocol can be useful.
621 We encourage early dialogue with us.

622
623 There are CMC changes where a preapproval inspection may be conducted prior to distribution of
624 product made with the change to confirm an acceptable cGMP compliance status.¹⁸ You may consult
625 the guidance documents listed in section II.E, or consult FDA, to determine whether FDA would
626 require such a preapproval inspection. If a preapproval inspection would be needed, your comparability
627 protocol would identify the preapproval inspection requirement and acknowledge that product made at
628 a different drug substance or different drug product manufacturing site will not be distributed until FDA
629 has verified the satisfactory cGMP compliance status for the type of operation at the new site.
630 Furthermore, in the case of aseptically processed product, your protocol would also provide that a
631 product manufactured in a different facility or area (e.g., room or building on a campus) will be
632 distributed only when that specific facility or area has a satisfactory cGMP compliance status. For a
633 move to another type of site (e.g., drug substance intermediate manufacturing site, packaging, testing
634 laboratory), the protocol would provide that a product manufactured at the site would not be distributed
635 if there were an unsatisfactory cGMP compliance status for the site.

636
637 For BLAs, some major changes at an existing facility (i.e., those that have a substantial potential to
638 adversely affect the product) may require, under 21 CFR 601.2(d), a satisfactory cGMP compliance
639 status prior to distribution of the product made with the change. For these major changes the
640 comparability protocol would provide that the product would not be distributed if an unsatisfactory
641 cGMP compliance status exists.

642
643 A comparability protocol has been beneficial when introducing additional products into an approved
644 dedicated area in a facility for biologics and protein drug products. In addition, for products with
645 facility/establishment information provided in a BLA or postapproval supplement to a BLA, (i.e.,
646 Establishment Description section), FDA may be limited in its ability to designate a reduced reporting
647 category for changes that include:

- 648
649
- 650 • Major changes in equipment, or utilities (e.g., new heating ventilation and air conditioning
651 system; new filling line for aseptically processed sterile products; in some limited instances
652 duplicative, discrete changes may be appropriate for a reduced reporting category (e.g.,
extensive modification of an existing Water For Injection system); or

¹⁸ A satisfactory cGMP compliance status includes a satisfactory cGMP inspection - an FDA inspection during which (1) no objectionable conditions or practices were found (No Action Indicated (NAI)) or (2) objectionable conditions were found, but, corrective action is left to the firm to take voluntarily and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI), and satisfactory disposition of other relevant actions (e.g., investigations, warning letter, product recalls).

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- 653 • The introduction of additional product(s) into an approved product-dedicated manufacturing
654 area of a facility where containment is a concern (e.g., live virus manufacturing operations such
655 as replication competent gene therapy vector propagation, or live attenuated viral vaccine
656 finishing operations).

657
658 **F. Can a Comparability Protocol Be Used for Container Closure System**
659 **Changes?**

660
661 Yes. In the past, applicants have used protocols for container closure system changes, and they can
662 continue to use them. A comparability protocol can be particularly useful for repetitive container closure
663 system changes.

664
665 **G. Can Implementation of or Changes in Process Analytical Technology (PAT) Be**
666 **Addressed in a Comparability Protocol?**

667
668 We anticipate that implementation of, or changes in, PAT could be addressed in a comparability
669 protocol. We encourage early dialogue with us. We intend to publish a PAT guidance in the future.

670
671 **H. Can a Master File Be Cross-Referenced in an Applicant's Comparability**
672 **Protocol?**

673
674 You can cross-reference a master file in a comparability protocol that provides for CMC changes (e.g.,
675 container resin). We recommend that you include, in the protocol, a commitment to provide a letter
676 authorizing us to review the master file when a postapproval CMC change implemented using the
677 approved comparability protocol is reported to us. We recommend that you indicate in the
678 comparability protocol the type of information (e.g., manufacturing and formulation information for a
679 plastic resin) that will be referenced in the master file and the information that you will provide such as
680 the studies you will perform to demonstrate the suitability of the new material (e.g., conformance to
681 approved specification, compatibility studies, stability studies).

682
683 **I. Can a Comparability Protocol Be Included in a Master File?**

684
685 A comparability protocol can be included in a master file. The protocol can be cross-referenced for
686 CMC changes. In your PAS submission for your product, you must include a letter authorizing us to
687 review the master file (21 CFR 314.420(b)). Comparability protocols are product specific. Therefore,
688 in your PAS submission we recommend that you provide a comparability protocol that augments the
689 information provided in the master file by specifying, for example, any additional studies that you will
690 perform to demonstrate the suitability of the postchange material (e.g., conformance to approved
691 specification, compatibility studies, stability studies). Ordinarily, we neither independently review master
692 files nor approve nor disapprove submissions to a master file.