Guidance for Industry

Comparability Protocols — Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
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CMC

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Guidance for Industry[1]

Comparability Protocols — Chemistry, Manufacturing, and Controls Information

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If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale and/or justification for the proposed revision.*
- *Identify specific comments by line numbers; use the pdf version of the document whenever possible.*
- *If possible, e-mail an electronic copy (Word) of the comments you have submitted to the docket to* **cunninghamp@cder.fda.gov**

I. INTRODUCTION

This guidance provides recommendations to applicants on preparing and using comparability protocols for postapproval changes in chemistry, manufacturing, and controls (CMC). The guidance applies to comparability protocols that would be submitted in new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), or supplements to these applications, except for applications for protein products.[2] Well-characterized synthetic peptides submitted in these applications are included within the scope of this guidance. This guidance also applies to comparability protocols submitted in drug master files (DMFs) and veterinary master files (VMFs) that are referenced in these applications.[3] The FDA is providing this guidance in response to requests from those interested in using comparability protocols.

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

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

[3] A separate guidance will address comparability protocols for proteins as well as for peptide products outside the scope of this guidance that are submitted in these applications. This separate guidance will also address comparability protocols for products submitted in biologics license applications (BLAs).

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

II. BACKGROUND

As an applicant, you are responsible for assessing, prior to distribution of a product, the effect of any postapproval CMC changes on the identity, strength, quality, purity, and potency of the product as these factors relate to the safety or efficacy of the product (section 506A(b) of the Federal Food, Drug, and Cosmetic Act (the act)). Such an assessment often includes demonstration that the pre- and postchange products (i.e., products manufactured prior to and subsequent to a change) are equivalent. Postapproval CMC changes must be reported to FDA in one of four reporting categories (Section 506A of the Act):

- Annual Report (AR)

The annual submission to the approved application reporting changes that FDA has identified as having 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-Effected Supplement (CBE)

A submission to an approved application reporting changes that FDA has identified as having 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 must be received by FDA before or concurrently with distribution of the product made using the change.

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

A submission to an approved application reporting changes that FDA has identified as having 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 must be received by FDA at least 30 days before distribution of the product made using the change.

- Prior Approval Supplement (PAS)

A submission to an approved application reporting changes that FDA has identified as having 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. A PAS supplement must be received and approved by FDA prior to distribution of the product made using the change.

In many cases, using a comparability protocol will facilitate the subsequent implementation and reporting of CMC changes, which could result in moving a product into distribution sooner than if a protocol were not used.

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

- the manufacturing process
- analytical procedures[4]
- manufacturing equipment
- manufacturing facilities
- container closure systems
- process analytical technology (PAT)

The guidance also discusses submitting comparability protocols in master files.

A. What is a Comparability Protocol?

A comparability protocol is a well-defined, detailed, written plan for assessing the effect of specific CMC changes in the identity, strength, quality, purity, and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. A comparability protocol describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is optional.

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

At the time the application containing the comparability protocol is approved, the FDA can designate,[5] where appropriate, a reduced reporting category for future reporting of CMC changes covered by the approved comparability protocol (see III.A). Furthermore, because a detailed

[4] The term *analytical procedure*, as used in this guidance, includes chemical, physical, microbiological, and biological test procedures.

[5] 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 V.A.6.

plan will be provided in the comparability protocol, the FDA is less likely to request additional information to support changes made under the protocol (see IV.D for a potential exception). The use of a comparability protocol could allow an applicant to implement CMC changes and place a product in distribution sooner than without the use of a comparability protocol.

C. Why is a Guidance on Comparability Protocols Being Provided?

For many years, applicants have used protocols to implement certain types of CMC changes, such as to extend an expiration dating period or to demonstrate the interchangeability of certain plastic containers. More recently, there have been many improvements in the techniques for characterizing products, production methods, process controls, and release testing. Because of these improvements and because we are able to better assess the potential effect of CMC changes on a product, protocols are now being used with other types of CMC changes (e.g., manufacturing process, analytical procedure). We have received a number of requests for guidance from applicants interested in using comparability protocols for these other types of changes.

D. Where Can More Information on Postapproval Changes and Demonstration of Equivalence Be Found?

This guidance, once finalized, is not intended to supersede other FDA guidance documents, rather it supplements them with information on using comparability protocols to implement postapproval CMC changes. We recommend that applicants consult all relevant guidances[6] for information relating to postapproval changes. The following guidances provide especially relevant information on (1) demonstrating equivalence, (2) documentation to be provided to support postapproval changes, and (3) the recommended reporting categories.

- *Changes to an Approved NDA or ANDA*
- *Changes to an Approved NADA or ANADA* (draft)[7]
- Various SUPAC documents[8]

[6] 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

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

[8] SUPAC (Scale-up and Post-Approval Changes)

144 **III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL**
145
146 **A. How Does a Comparability Protocol Affect the Reporting of CMC Changes?**
147
148 A comparability protocol *prospectively* specifies the tests and studies that will be performed,
149 analytical procedures that will be used, and acceptance criteria that will be achieved to assess the
150 effect of CMC changes. A well-planned protocol provides sufficient information for FDA to
151 determine whether the potential for an adverse effect on the product can be adequately evaluated.
152 With a comparability protocol, the FDA can determine if a specified change can be reported in a
153 category lower than the category for the same change, were the change to be implemented
154 without an approved comparability protocol. Typically, categories designated for reporting
155 changes under an approved comparability protocol are one category lower than normally would
156 be the case (e.g., from PAS to CBE-30, CBE, or AR). In some cases, a reduction of more than
157 one reporting category may be possible (e.g., PAS to AR).
158
159 **B. When Might a Comparability Protocol Be Useful for a CMC Change?**
160
161 A comparability protocol could be useful for a variety of CMC changes, but there are some
162 exceptions (see Section III.C). In addition, a comparability protocol can describe a single CMC
163 change or multiple related changes. However, we recommend that each change be discrete and
164 specific. A comparability protocol can be particularly useful for changes of a repetitive nature.
165 We recommend that you have sufficient manufacturing information (e.g., developmental studies,
166 manufacturing experience, demonstrated process capability, out-of-specification (OOS)
167 investigations, stability data) with the particular product or process or similar products or
168 processes so you can specify a priori the tests, studies, analytical procedures, and acceptance
169 criteria appropriate for demonstrating that the CMC change or changes will not adversely affect
170 the product. We recommend that comparability protocols be considered for CMC changes that
171 applicants anticipate will be made.
172
173 We recommend you consider product-specific and process-specific attributes when determining
174 whether to develop a comparability protocol. Attributes can include, but are not limited to, the
175 following:
176
177 - Complexity of the product structure
178 - Ability to characterize the chemical, physical, microbiological, and biological
179 properties of the product
180 - Degree to which differences in product structure and physical properties (e.g.,
181 polymorph) can be detected
182 - Degree of product heterogeneity if present
183 - The effect on safety of changes in the impurities
184 - The robustness of the product (i.e., the ability of product to remain unaffected by
185 changes)

- Rigorousness of the manufacturing process controls (i.e., the ability of the manufacturing process controls to ensure that the product remains unaffected by changes)

In general, we recommend that a comparability protocol be considered only if the product resulting from the changes is expected to meet the approved drug substance and/or drug product specifications and appropriate and sensitive analytical procedures have been established and validated or qualified (i.e., for nonroutine tests such as characterization studies) to detect the effect of the change on the approved product.

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 a priori. 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:

- Broad, nonspecific plans for CMC changes
- A change whose 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 IND,[9] INAD, or new original application.
- 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)

It may be possible to design a comparability protocol for some of these CMC changes, but FDA may be limited in its ability to designate a reporting category other than PAS for changes implemented under such a protocol. Specific examples of changes that may be difficult to justify under a comparability protocol can include[10]:

- A change in the drug substance or drug product specifications (for exceptions, see V.A.4 and V.C)

[9] INDs may be warranted in certain circumstances, such as for a change from a nontransgenic source to a transgenic plant or animal, a change from one plant or animal transgenic source material to another, or a change in the species of a microorganism or cell line used as source.

[10] In some situations, these changes could warrant the submission of an IND, INAD, or new application.

- A change in the qualitative or quantitative formulation of the drug product.[11]
- A change in the type of delivery system
- 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 from synthesis-derived to naturally sourced material and vice versa
- A change from solid phase to liquid phase peptide synthesis and vice versa
- A move to a manufacturing site, facility, or area when a prior approval supplement is recommended because a current good manufacturing practice (CGMP) inspection is warranted (e.g., see examples in guidances listed in II.D.)

IV. PROCEDURES FOR COMPARABILITY PROTOCOLS

A. How Should a Comparability Protocol Be Submitted?

You can submit a comparability protocol in a prior approval supplement or as part of the original application. We recommend that you indicate clearly in the cover letter that you are submitting a comparability protocol.

The submission can consist of the proposed comparability protocol in

- A prior approval supplement that is reviewed and approved prior to generating data supporting the change
- A prior approval supplement that includes the proposed comparability protocol and test and study results as specified in the proposed comparability protocol and any other pertinent information to support a change covered under the protocol. The product already manufactured with the change can be distributed only after approval of the supplement.
- An original application that is reviewed and approved prior to generating data supporting the change

In all cases, a comparability protocol would be reviewed and approved by FDA prior to an applicant implementing a change under the protocol. Furthermore, an applicant who is using an approved comparability protocol to implement postapproval CMC changes must assess the effect of the changes on the identity, strength, quality, purity, and potency of the product as these

[11] 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 (e.g., quantitative changes in an excipient beyond the ranges specified in the SUPAC guidances).

258 factors relate to the safety or efficacy of the product prior to distributing product made with the
259 change. (Section 506A(b) of the act)).
260
261 **B. How Are Changes and Study Results Submitted After a Comparability**
262 **Protocol is Approved?**
263
264 After a protocol is approved, you should document and submit each implemented change within
265 the scope of the protocol using the reporting category designated by FDA. The submission
266 would include (1) the results of all tests and studies specified in your comparability protocol, (2)
267 discussions of any deviations that occurred during the tests or studies, (3) a summary of any
268 investigations performed, and (4) any other pertinent information. To ensure prompt and
269 accurate review, we recommend that you indicate in the cover letter to the submission that it
270 includes data from a change covered under a comparability protocol and provide a reference to
271 the submission in which the comparability protocol was approved.
272
273 **C. What If Study Results Do Not Meet the Criteria Specified in the Approved**
274 **Comparability Protocol?**
275
276 In certain instances, the tests and studies specified in an approved comparability protocol can
277 lead to an unpredicted or unwanted outcome (e.g., test results do not meet predefined acceptance
278 criteria). If this occurs, you can elect not to implement the change. If you decide to pursue the
279 change, you should submit a prior approval supplement that provides the supporting data to
280 justify why the change will not adversely affect the identity, strength, quality, purity, and
281 potency of the specific drug product as these factors relate to the safety and effectiveness of the
282 product.
283
284 **D. When Does a Comparability Protocol Become Obsolete?**
285
286 New regulatory requirements, identification of a safety issue (e.g., screening for new infectious
287 agents in materials from a biological source), identification of a new scientific issue, or
288 technological advancement after the comparability protocol has been approved can render a
289 protocol obsolete. We recommend you review the tests, studies, analytical procedures, and
290 acceptance criteria in your approved comparability protocol to ensure they remain current and
291 consistent with the approved application and current FDA policy. We recommend you
292 determine whether the tests, studies, analytical procedures, and acceptance criteria described in
293 your comparability protocol are still appropriate prior to implementing and submitting a change
294 under the protocol. If you find the comparability protocol is no longer correct or adequate, the
295 current protocol should be modified or withdrawn. FDA can request additional information to
296 support a change that is implemented using an obsolete protocol.
297
298 **E. How is an Approved Comparability Protocol Modified?**
299
300 You can submit a revised protocol at anytime. Like an original protocol, a revised protocol
301 should be submitted as a PAS to your application following the recommended submission
302 procedures summarized in section IV.A. To ensure prompt and accurate review, we recommend

that you indicate in the cover letter to the submission that it includes a revision to an approved comparability protocol and identify all modifications.

A comparability protocol would be modified to reflect relevant changes in the application. For example, an applicant could request a change in an analytical procedure that is used for release testing but is also cited in an approved comparability protocol. As part of the request to make such a change, FDA recommends that the applicant indicate up front all comparability protocols that will be affected. The specified comparability protocols can be updated as part of this submission using the appropriate reporting category for the change, rather than submitting a separate submission requesting a modification of the comparability protocol. Revisions to a protocol should be approved prior to distributing the product made using the CMC change specified in the protocol.

Editorial changes can also be made. Notification of editorial changes to a comparability protocol can be provided in the AR.

V. CONTENT OF A COMPARABILITY PROTOCOL[12]

We recommend that a comparability protocol be developed and used within the context of existing change control procedures. Such procedures ensure that specified changes do not adversely affect the identity, strength, quality, purity, or potency of the product.

The comparability protocol can describe a single CMC change or multiple changes. Each change should be specified and the acceptance criteria for evaluating the effect of the changes should be well defined. If multiple changes are included in a protocol, we recommend that the multiple changes be interrelated (i.e., one change cannot be made with out the others). For example, a change in a fermentation medium component used to produce an antibiotic can result in more rapid cell growth, which, in turn, causes a higher production rate of antibiotic. Changes related to this change in culture medium could include modification in the length of cell fermentation, increase in harvesting time, and/or changes to purification columns. We recommend that you submit separate comparability protocols for unrelated changes.

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

1. Description of the Planned Changes

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

[12] 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 application.

344 *2. Specific Tests and Studies to Be Performed*
345
346 A list should be included of the specific tests (e.g., release, in-process) and studies (e.g.,
347 characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or
348 inactivation) you will perform to assess the effect of the change on the drug substance, drug
349 product, and/or, if appropriate, the intermediate, in-process material, or component (e.g.,
350 container closure system) directly affected by the change. Include the rationale for selecting the
351 particular battery of tests and studies. For example, the use of nonroutine studies (e.g.,
352 characterization) can be warranted in cases where in-process or release specifications are not
353 sufficiently discriminatory to evaluate the change.
354
355 A protocol should include a plan to compare results from routine batch release testing and, as
356 appropriate, nonroutine testing (e.g., characterization studies) on pre- and postchange products or
357 other material, if appropriate. The protocol should specify the number and type (e.g., pilot,
358 production) of pre- and postchange batches and/or samples that will be compared. The number
359 and type of batches and/or samples to be compared can vary depending on the extent of the
360 proposed change, type of product or process, and available manufacturing information. Retained
361 samples of prechange material can be used for comparison, provided there is no significant
362 change in material on storage (e.g., level of degradants increasing over time). A plan would
363 specify whether retained samples are going to be used and the maximum age of the retained
364 samples, and include information to support the appropriateness of the use of retained samples.
365 In general, the results from postchange material should fall within the normal batch-to-batch
366 variation observed for prechange material.
367
368 A comparability protocol should include a plan for the stability studies that will be performed to
369 demonstrate the equivalence of pre- and postchange product. The comparability protocol would
370 provide (1) information that is typically provided in a stability protocol, such as the number and
371 type of batches that will be studied, test conditions, and test time points or (2) a reference to the
372 currently approved stability protocol. The amount of stability data that will be generated before
373 the product made with the change is distributed would be specified. The plan for evaluating
374 stability could vary depending on the extent of the proposed change, type of product, and
375 available manufacturing information. In some cases, no stability studies may be warranted or a
376 commitment to report results from stability studies in an AR can be sufficient. If no stability
377 studies are planned, we recommend that this be stated clearly.
378
379 The differences, if any, in the tests and studies from those previously reported in the approved
380 application or subsequent updates (i.e., supplements, annual reports) would be described. We
381 recommend you identify the location in your application of any referenced tests or studies.
382
383 *3. Analytical Procedures to be Used*
384
385 A protocol should specify the analytical procedures that you intend to use to assess the effect of
386 the CMC changes on the product or intermediate material. Analytical procedures would be
387 chosen capable of detecting new impurities or other changes in a product that can result from the
388 change.

389
390 Since the current approved analytical procedures are optimized for the approved product and
391 process, modified or new procedures may be warranted. For example, revised or new analytical
392 procedures can be called for to monitor the removal of a new process impurity generated by a
393 new manufacturing process. In this situation, submission of results for pre- and postchange
394 products using both the old and new analytical procedures may be warranted. Studies performed
395 to assess the feasibility of the proposed change can often be helpful in determining whether the
396 current approved analytical procedures will be appropriate for assessing the effect of the change
397 on the product (see V.A.5). Validation of new modified analytical procedures or revalidation of
398 existing analytical procedures should be performed, as appropriate. The protocol would specify
399 that any new or revised analytical procedures and the appropriate validation or revalidation
400 information would be provided when a postapproval CMC change implemented using the
401 approved comparability protocol is reported to FDA.
402
403 In some instances, analytical procedures are used in the characterization and/or assessment of the
404 functionality of a product, but not for batch release or for process control (e.g., X-ray
405 crystallography, plume geometry for metered dose inhalers). If these analytical procedures are
406 not routinely used for process or release testing, you do not have to report changes in these
407 analytical procedures (e.g., when they are used only for drug development). However, if these
408 analytical procedures are specified in and provided as part of a comparability protocol, any new
409 or revised analytical procedures and, as appropriate, results from validation or qualification
410 studies for any modified procedure would be provided when a postapproval CMC change
411 implemented using the approved comparability protocol is reported to FDA.
412
413 In cases where changes in analytical procedures are intended to be implemented independent of
414 other CMC changes, we recommend that a comparability protocol specific for analytical
415 procedure changes be submitted (see V.C)
416
417 *4. Acceptance Criteria*
418
419 You should include the acceptance criteria (numerical limits, ranges or other criteria) for each
420 specified test and study that will be used to assess the effect of the CMC changes on the product
421 or other material and/or demonstrate equivalence between pre- and postchange material. In
422 general, the drug substance and drug product specification would be identical to that in the
423 approved application. Any statistical analyses that will be performed and the associated
424 evaluation criteria would be identified.
425
426 If implementing a change using a comparability protocol calls for a revision of the drug product
427 or drug substance specification, we recommend you consider the recommended reporting
428 category[13] for the type of specification change as well as the designated reporting category for
429 reporting a change using your comparability protocol. When the recommended reporting
430 category for the specification change is higher (e.g., PAS) than the reporting category for

[13] For example, the recommended reporting categories for specification changes found in the guidance on *Changes to an Approved NDA or ANDA*.

431 changes made under the comparability protocol (e.g., CBE-30), the change would be reported as
432 recommended for the specification change. If the recommended reporting category for the
433 specification change is the same or lower than the designated reporting category for changes
434 made under the comparability protocol, the specification can be updated and provided when a
435 postapproval CMC change implemented using the approved comparability protocol is reported
436 to FDA.
437
438 *5. Data to Be Reported Under or Included With the Comparability Protocol*
439
440 You should identify the type (e.g., release, long-term or accelerated stability data) and amount of
441 data (e.g., 3-months accelerated stability data) that will be submitted at the time a postapproval
442 CMC change implemented using the approved comparability protocol is reported to FDA and,
443 when appropriate, generated prior to your distributing the product made with the change (e.g.,
444 when proposed reporting category is a CBE-30, CBE-0, or AR).
445
446 If available, you can include any data from studies performed to assess the feasibility of the
447 proposed change with the proposed comparability protocol. Data obtained from a small-scale
448 process or other studies incorporating the proposed change can provide preliminary evidence that
449 the change is feasible, as well as preliminary information on the effect of the change on the
450 product. Development or feasibility studies can provide insight into the relevance and adequacy
451 of the choice of the battery of tests you have identified to assess the product.
452
453 *6. Proposed Reporting Category*
454
455 The use of an approved comparability protocol may justify a reduction in the reporting category
456 for the particular CMC change when implemented (see III.A). We recommend you include a
457 proposal for the reporting category that you would use for changes implemented using the
458 approved comparability protocol. FDA will evaluate your proposed reporting category as part of
459 its review of the comparability protocol and communicate any concerns about your proposal.
460 Agreement by the applicant and FDA on the reporting category for the specified CMC changes
461 will be part of the process of approving the comparability protocol.
462
463 *7. Equivalence Not Demonstrated Using the Approved Comparability Protocol*
464
465 It is anticipated that some changes in the manufacturing process will result in a postchange
466 product that cannot be demonstrated to be equivalent to the prechange product without more
467 extensive physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a
468 product that does not meet the prespecified acceptance criteria in the protocol. You should
469 identify in the protocol the steps you will take in such circumstances.
470
471 *8. Commitment*
472
473 You should include a commitment in your comparability protocol that you will update or
474 withdraw your protocol when it becomes obsolete (see section IV.D)
475

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

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

1. Comparison of Physical Characteristics

A comparability protocol would normally include a plan to compare the physical characteristics (e.g., polymorph forms, particle size distribution) of the product produced using the old and new processes when these characteristics are relevant to the safety and/or efficacy of the product.

2. Comparison of Impurity Profiles

A comparability protocol would include a plan to determine the impurity profile of the product produced using the new process. The studies would assess product-related impurities and process-related impurities, including, if applicable in-process reagents and catalysts. We recommend that attention be given to demonstrating the absence of any new impurities or contaminants, or that they are removed or inactivated by downstream processing. Any changes in the impurity profile would meet the predefined criteria (see section V.A.4). The predefined criteria would indicate when qualification studies will be warranted to evaluate an increased level of an existing impurity or a new impurity (or an applicant could reference a relevant FDA guidance that recommends qualification levels).

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

3. Effect on Downstream Processes

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

514 4. *Effect on Process Controls and Controls of Intermediates and/or In-process*
515 *Materials*
516
517 We recommend you identify and justify implementation of new controls or variations from
518 approved controls. We recommend a statement be included that controls, including those that
519 have been validated to inactivate and remove impurities or contaminants, will be revalidated for
520 the new production process, if appropriate.
521
522 **C. Does FDA Have Specific Concerns About Changes in Analytical Procedures**
523 **That Should Be Addressed in a Comparability Protocol?**
524
525 A comparability protocol for changing an analytical procedure would provide the plan for
526 validation of the changed analytical procedure and indicate whether the protocol will be used to
527 modify the existing analytical procedure (i.e., retaining the same principle), or to change from
528 one analytical procedure to another (e.g., normal to reverse phase HPLC). The comparability
529 protocol would be designed to demonstrate that the proposed changes in the analytical
530 procedures improve or do not significantly change characteristics used in methods validation that
531 are relevant to the type of analytical procedure (e.g., accuracy, precision, specificity, detection
532 limit, quantitation limit, linearity, range).[14]
533
534 Methods validation includes an assessment of the suitability of the analytical procedure. A
535 validation plan would have prespecified acceptance criteria for relevant validation parameters
536 such as precision, range, accuracy, specificity, detection limit, and quantitation limit. The
537 proposed acceptance criteria for these parameters would ensure that the analytical procedure is
538 appropriate for its intended use. The validation plan would assess whether a revised procedure is
539 more susceptible than the original procedure to matrix effects by process buffers/media, product-
540 related contaminants, or other components present in the dosage form. A plan would identify
541 any statistical analyses that will be performed and whether product testing to compare the two
542 procedures is intended. The need and plan for providing product testing to compare the two
543 procedures could vary depending on the extent of the proposed change, type of product, and type
544 of test (e.g., chemical, biological).
545
546 When used for release or process control, use of the new revised analytical procedure should not
547 result in deletion of a test or relaxation of acceptance criteria that are described in the approved
548 application.
549
550 **D. Does FDA Have Specific Concerns About Changes in Manufacturing**
551 **Equipment That Should Be Addressed in a Comparability Protocol?**
552

[14] Guidance on validation of 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* .

553 Comparability protocols may be most useful if applicants are planning to change to equipment
554 with a different operating principal. Equipment changes are often made in conjunction with
555 changes to the manufacturing process. We recommend that you evaluate this type of change
556 with respect to its effect on the production process prior to deciding whether or not a
557 comparability protocol would be appropriate.
558
559 **E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities**
560 **That Should Be Addressed in a Comparability Protocol?**
561
562 The utility of a comparability protocol is often limited due to the scope of the change and the
563 need, in some cases, for an inspection. For example, a move to a new facility can involve many
564 changes (e.g., new equipment, modified manufacturing process) that are difficult to
565 prospectively identify as part of a comparability protocol because the new facility is unknown or
566 not constructed at the time the comparability protocol is being considered. We recommend you
567 consider carefully the appropriateness of a comparability protocol for a facility change that
568 involves many other changes.
569
570 We recommend a statement be included in the comparability protocol for changing
571 manufacturing facilities saying that a move to a different drug substance or drug product
572 manufacturing site will be implemented only when the site has a satisfactory CGMP inspection
573 for the type of operation. Furthermore, in the case of aseptically processed product, the
574 statement would also indicate that a move to a different facility or area (e.g., room or building on
575 a campus) will be made only when the specific facility or area has a satisfactory CGMP
576 inspection (irrespective of the overall CGMP status for the campus). For a move to another type
577 of site (e.g., drug substance intermediate manufacturing site, testing laboratory), a statement
578 would be included that the move to this site would not be implemented if there were an
579 unsatisfactory CGMP inspection for the site.[15]
580
581 **F. Can a Comparability Protocol Be Used for Container Closure System**
582 **Changes?**
583
584 In the past, applicants have used protocols for container closure system changes, and they can
585 continue to use them. A comparability protocol can be particularly useful for repetitive
586 container closure system changes.
587
588 **G. Can Implementation of or Changes in Process Analytical Technology (PAT)**
589 **Be Addressed in a Comparability Protocol?**
590

[15] A satisfactory CGMP inspection is 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)).

591 FDA anticipates that implementation of or changes in PAT could be addressed in a
592 comparability protocol. Early dialogue with FDA is encouraged. The FDA intends to publish a
593 guidance on PAT in the future.
594
595 **H. Can a DMF or VMF Be Cross-Referenced in an Applicant's Comparability**
596 **Protocol?**
597
598 A master file can be cross-referenced in a comparability protocol that provides for CMC changes
599 (e.g., new manufacturer of drug substance, container resin). The protocol would include a
600 commitment to provide a letter authorizing the FDA to review the master file when a
601 postapproval CMC change implemented using the approved comparability protocol is reported
602 to FDA. The comparability protocol would also indicate the type of information (e.g.,
603 manufacturing and formulation information for a plastic resin) that will be referenced in the
604 master file and the information that you will provide such as the studies you will perform to
605 demonstrate the suitability of the new material (e.g., conformance to approved specification,
606 compatibility studies, stability studies).
607
608 **I. Can a Comparability Protocol Be Included in a DMF or VMF?**
609
610 A comparability protocol can be included in a master file. The protocol can be cross-referenced
611 for CMC changes. An applicant's submission must include a letter authorizing the FDA to
612 review the master file (e.g., 21 CFR 314.420(b)). Comparability protocols are product specific.
613 Therefore, the applicant's submission would provide a comparability protocol that augments the
614 information provided in the master file by specifying, for example, any additional studies that
615 will be performed to demonstrate suitability of the postchange material (e.g., conformance to
616 approved specification, compatibility studies, stability studies). The FDA ordinarily neither
617 independently reviews master files nor approves or disapproves submissions to a master file.