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Draft — Not for Implementation

Guidance for Industry[1]

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 products[2] 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

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

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

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

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 they may relate to the safety or efficacy of the product). Such an assessment often includes data that demonstrate that the pre- and post-change products (i.e., the products manufactured prior to and subsequent to a manufacturing change) are comparable. You must report postapproval CMC changes to FDA, us, in one of the reporting categories described by FDA (section 506A(b) of the Federal Food, Drug, and Cosmetic Act (the act) (21 USC 356a).[6] (See II.E for references). As part of its review and approval of a comparability protocol to evaluate the effects of a change, if supported by the submission, FDA may determine that a CMC change made under the comparability protocol will fall into a less restrictive reporting category. 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 submitted.

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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.

58
59 • Annual Report (AR)
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61 This annual submission to the approved application reports changes that have minimal potential to
62 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
63 the safety or effectiveness of the product.
64
65 • Change-Being-Effected Supplement (CBE)
66
67 This submission to an approved application reports changes have moderate potential to adversely
68 affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety
69 or effectiveness of the product. A CBE supplement would be received by FDA before, or
70 concurrently with, distribution of the product made using the change. It is distinguishable from a
71 Change-Being-Effected-in-30-Days Supplement (discussed below) because FDA has determined
72 that, based on experience with a particular type of change, the supplement for such change is usually
73 complete and provides the proper information, and based on assurances that the proposed change
74 has been appropriately submitted, the product made using the change may be distributed
75 immediately upon receipt of the supplement by FDA.
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77 • Change-Being-Effected-in-30-Days Supplement (CBE-30).
78
79 This submission to an approved application reports changes that have moderate potential to
80 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
81 the safety or effectiveness of the product. A CBE-30 supplement would be received by FDA at
82 least 30 days before you may distribute the product made using the change (21 CFR 601.12(c)(3)).
83
84 • Prior Approval Supplement (PAS)
85
86 This submission to an approved application reports changes that have a substantial potential to
87 adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to
88 the safety or effectiveness of the product. FDA would receive and approve a PAS before you may
89 distribute the product made using the change (21 CFR 601.12(b)).
90
91 This guidance describes the general principles and procedures associated with developing and
92 submitting a comparability protocol to us. This guidance also describes the basic elements of a
93 comparability protocol and specific issues to consider when developing comparability protocols for
94 changes in:
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- the manufacturing process,
- analytical procedures,[7]
- manufacturing equipment,
- manufacturing facilities,
- container closure systems, and
- process analytical technology (PAT).

This 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 on the identity, strength, quality, purity, and potency of a specific drug product as they may 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 met to demonstrate that specified CMC changes do not adversely affect the product. The submission of a comparability protocol is not required to make a CMC change.

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

At the same time we approve a comparability protocol, we can designate,[8] if appropriate, a reduced reporting category for future reporting of CMC changes covered by the approved comparability protocol (See section III.A). Furthermore, because a detailed plan will be provided in the comparability protocol, we are less likely to request additional information to support changes made under the protocol (See section 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. When and Why Were Comparability Protocols Created?

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 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.

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 changes). This expanded use of comparability protocols has been recognized in FDA regulations,[9] and we have received a number of requests for guidance from applicants interested in using comparability protocols for these other types of changes. The use of comparability protocols for expanded types of CMC changes has allowed some applicants to implement CMC changes sooner.

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

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

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

This guidance is not intended to supersede other FDA guidance documents, but rather to supplement them with information on using comparability protocols to implement postapproval CMC changes. We recommend that you consult all relevant guidances[10] for information relating to postapproval changes. The following guidances provide relevant information on: (1) assessing the effect of CMC changes on product attributes, (2) providing documentation to support postapproval change, and (3) the recommended reporting categories.

- *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products Including Therapeutic Biotechnology-derived Products, (April 1996)*
- *Guidance For Industry: Changes to an Approved Application For Specified Biotechnology and Specified Synthetic Biological Products (July 1997)*
- *Guidance For Industry: Changes to an Approved Application For Biological Products (May 1996)*
- *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an Approved NDA or ANDA*[11] (November 1997)
- *Guidance For Industry: Chemistry Manufacturing and Controls Changes to an Approved NADA or ANADA* (draft) [10, 12] (June 1999)

[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.

III. WHAT TO CONSIDER IN PLANNING A COMPARABILITY PROTOCOL

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

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

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

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

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

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

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

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

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

- Increase or decrease in batch size that affects equipment size,
- Modification of production operating parameters in fermentation (e.g., time, temperature, pH, dO_2 (dissolved oxygen)),
- Adding, deleting, or substituting raw materials (e.g., buffer or media components),
- Mode changes (usually associated with equipment changes such as tangential flow filtration to centrifugation),
- Establishing a new working cell bank using a modified procedure,
- Reprocessing the drug substance or drug product, as appropriate,
- Addition, deletion, or rearrangement of production steps; and
- Facility-related changes for products with facility/establishment information provided in a BLA, or postapproval supplement to a BLA (see examples provided in Section V. E.).

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.

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

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

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. However, we recommend that you evaluate the appropriateness of including the comparability protocol in the original application when your experience manufacturing the product is limited and it may be difficult to identify the elements of an appropriate comparability protocol (see considerations in Section III.B.). We recommend that you indicate that you are submitting a comparability protocol.

You may submit the proposed comparability protocol in:

- A prior approval supplement that consists only of the proposed comparability protocol. You may want us to review and approve the protocol and determine the reporting category for changes, evaluated under the protocol, prior to generating data specified in the protocol.
- A prior approval supplement that includes the proposed comparability protocol, study results, and any other pertinent information as specified in the proposed comparability protocol. Note that the comparability data submitted would be evaluated as part of the prior approval supplement. The product already manufactured with the change can be distributed only after approval of the supplement.
- A part of an original market application. You may want the comparability protocol reviewed and approved and the reporting category determined, prior to generating data specified in the protocol.

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

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.

E. How is an Approved Comparability Protocol Modified?

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

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

V. CONTENT OF A COMPARABILITY PROTOCOL[15]

We recommend that that you develop and use a comparability protocol 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.

In the comparability protocol, you can describe a single CMC change or multiple changes. We recommend that you specify each change and define the acceptance criteria for evaluating the effect of the changes. If multiple changes are included in a protocol, we recommend that the multiple changes be interrelated (i.e., one change cannot be made without the others; changes focus on a common goal such as production optimization). For example, a change in a fermentation medium component used to produce a protein results in more rapid cell growth that in turn, causes a higher production rate of the protein. 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.

[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.

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.

2. Specific Tests and Studies to Be Performed

We recommend that you include a list of the specific tests (e.g., release, in-process) and studies (e.g., characterization, stability, removal of impurities, laboratory-scale adventitious agent removal or inactivation, validation, process development) that you will perform to assess the effect of the change on the drug substance, drug product, and/or, if appropriate, the intermediate, in-process material, or component (e.g., container closure system) directly affected by the change. We recommend that you include the rationale for selecting the particular battery of tests and studies. This rationale could include a discussion of the type and extent of the change, potential effect of the change, experience with the manufacturing process, and product robustness. For example, the inclusion of additional tests to check for new impurities, glycosylated species or other posttranslation modifications that may be formed as a result of the change, or use of nonroutine studies (e.g., characterization) may be warranted. Such additional testing is especially important in cases where in-process or release specifications are not sufficiently discriminatory to evaluate the change, (e.g., tests for secondary or tertiary structure). We recommend that you include a plan, within the protocol, to compare results from routine batch release testing and, as appropriate, nonroutine testing (e.g., characterization studies) on pre- and postchange products or other material, if appropriate. We recommend that you specify the number and type (e.g., pilot, production) of pre- and postchange batches and/or samples that will be compared. The number and type of batches and/or samples to be compared can vary depending on the extent of the proposed change, type of product or process, and available manufacturing information. You can use retained samples of prechange material for comparison, provided there is no significant change in material during storage (e.g., level of degradants increasing over time). If you plan to use retained samples, we recommend that you specify their maximum age and provide a justification with supporting data for using retained samples. In general, the results from postchange material should fall within the normal batch-to-batch variation observed for prechange material.

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

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

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

3. Analytical Procedures to Be Used

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

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

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

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

4. Acceptance Criteria

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

After implementing a change under a comparability protocol, you may find that the CMC change calls for a revision of the drug product or drug substance specification. Change to that specification under these circumstances would not fall under the determination of reporting category made for the comparability protocol submission. Accordingly, in making your CMC change submission, we recommend that you consider the recommended reporting category[16] for the type of specification change as well as the designated reporting category for reporting a change using your comparability protocol. When the recommended reporting category for the specification change is higher (e.g., PAS) than the reporting category for changes made under the comparability protocol (e.g., CBE-30), we recommend that you use the reporting category associated with the specification change, that is, the higher reporting category. If the recommended reporting category for the specification change is the same or lower than the designated reporting category for changes made under the comparability protocol, the specification can be updated and provided when you report a postapproval CMC change implemented using the approved comparability protocol.

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

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

If available, you can include any data from studies performed to assess the feasibility of the proposed change with the proposed comparability protocol. Data obtained from a small-scale process or other 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.*

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

6. Proposed Reporting Category

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

7. Comparability Not Demonstrated Using the Approved Comparability Protocol

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

8. Commitment

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

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 related to changes in the manufacturing process, where applicable:

1. Physicochemical and Biological Characterization

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

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

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.
596
597 **D. Does FDA Have Specific Concerns About Changes in Manufacturing**
598 **Equipment That Should Be Addressed in a Comparability Protocol?**
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.
609
610 **E. Does FDA Have Specific Concerns About Changing Manufacturing Facilities**
611 **That Should Be Addressed in a Comparability Protocol?**
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*.

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

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

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

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

- Major changes in equipment, or utilities (e.g., new heating ventillation and air conditioning system; new filling line for aseptically processed sterile products; in some limited instances 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).

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

F. Can a Comparability Protocol Be Used for Container Closure System Changes?

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

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

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

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

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

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

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

添付資料2

ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

Notice to the Reader: Where reference is made to nonclinical and clinical studies, additional information and modification of these specific items will be provided by ICH Safety and Efficacy Experts.

1.0 Introduction

1.1 Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. This guideline is intended to assist in the design and conduct of studies used to collect the technical information to establish the comparability of pre-change and post-change products and, thereby, confirm that the manufacturing process changes did not have an adverse impact on the quality, safety and efficacy of the drug product.

1.2 Background

Manufacturers [1] of biotechnological/biological products frequently make changes to manufacturing processes [2] of products [3] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between pre-change and post-change products, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes (see References). This document builds upon the previous ICH guidelines and provides additional direction regarding approaches to:

- Compare post-change product to pre-change product following manufacturing process changes and
- Assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy.

[1] For convenience, when the term "manufacturer" is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).
[2] For convenience, when the term "manufacturing process(es)" is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.
[3] For convenience, when the term "product" is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.