同質性評価といえば、当初は安全性、有効性評価試験を繰り返すことなく同等性／同質性を担保するための評価法の検討が目的であった。しかし最近の欧米の議論は、製造方法の変更によって製品の品質に変化が生じた場合に、治療薬としての安全性、有効性に悪影響がないことをどのように評価するか、という方向に目的が変質しているように思われる。このことが、未だ作成していない日本における同等性／同質性評価法ガイドラインを考える上で、欧米との調和に困難をもたらす原因になりつつあるように思われる。

前臨床試験および臨床試験についても、欧米の最近の傾向からすると、同等性／同質性評価において、ブリッジング臨床研究程度は行わなければならない事例を想定して議論を行う傾向になっているように思われる。この点、筆者は、同等性／同質性評価の原点に戻って整理する必要があると考える。即ち、製造方法の変更によって新たな不純物が生じた場合は、その不純物について安全性を確認するための動物実験等は必要であろう。またアミノ酸の一次配列はともかく、高次構造については十分な解析が可能なような分析手段がないタンパク質性医薬品においては、同等性／同質性を示すためにヒトにおける免疫原性試験、および製剤の生物学的同等性を評価するためのヒトにおける血中動態試験による同等性の検討が必要な場合も少なくないと思われる。しかし、臨床での有効性についての同等性を評価するための臨床試験を行わなければならないほど、品質に変化が現れた場合には、変更された製造方法で製造された医薬品は同等性／同質性評価の対象とせずに、新薬の評価基準に従って評価するという割り切りが必要と考えられる。

6．　まとめ、結論

米国 FDA では、同等性／同質性評価プロトコールの運用とともにその更なる整備を進めており、最近になってタンパク質性医薬品以外の医薬品（Generic Drugs も含めた）についても同等性／同質性評価プロトコールに関するガイダンスを作成した。内容的には、生物薬品に関するガイドラインと矛盾する点はない。

一方欧州 CPMP では 2002 年 3 月に施行したバイオ医薬品の同等性／同質性評価ガイドラインの補遺ドラフトを公表し、現在意見聴取期間にある。この補遺ドラフトでは、同等性／同質性評価ガイドライン本体では明確にできなかった、(1)非臨床試験および臨床試験の必要性に関する記述、(2)免疫原性試験に関する記述、(3)先発メーカーによる先発製品と同等なものとして後発メーカーから申請された後発品の同等性／同質性評価、の 3 点を主に扱っている。非臨床試験および臨床試験については一般的な原則を記述しており、内容は妥当なものと考えられる。ただし、実際の同等性／同質性評価は連続的、階層的な評価であり、その中で臨床試験は最終段階であり、本質的にケースバイケースの対応が求められるが、どのような場合に臨床試験が要求されるかについては、未だ明確な方向が示されておらず、実際に利用しようとしても利用しにくいガイダンスという印象をもたざるをえない。

CPMP の同等性／同質性ガイドラインの補遺ドラフトでは、ヒトにおける免疫原性試験の必要性を強調している。そのこと自体は重要な視点ではあるものの、免疫原性が問題となっている事例をみても、事故の発生頻度は極めて低く、免疫原性に関する臨床試験をあらかじめ行ってみても、予測性は低いものとならざるをえない。その点、実際の同等性／同質性評価において免疫原性試験の位置付けをどのようにとるかは今後の課題といえよう。

欧米とも、法律的には Generic Biologics（安全性および有効性については文献を参照することで申請者自身では前臨床試験および臨床

試験を行うことなく申請された医薬品）はないこととなっている（欧州は法律改正作業中）。CPMP の同等性／同質性評価ガイドラインの補遺ドラフトでは先発品と同等なものとして後発メーカーが申請してきた製品の同等性／同質性評価にふれているが、同一メーカーにおける製造方法が変更された製品間の比較の原則の延長線上にあり、妥当なものと考えられる。

7．　全体のまとめ

米国 FDA と欧州 CPMP の同等性／同質性評価の科学的アプローチには大きな差異はない。即ち、(1)製造方法の変更の前後の製品間についての、理化学的特性（不純物を含めた）および生物学的特性の比較、(2)新しい工程の工程内管理試験、および変更したプロセスの検証、(3)動物モデルを用いた体内動態等の試験（米国では(1), (2)によって同等性／同質性が確保された場合(3)は必ずしも必要とされないのに対し、欧州では(3)も行うという表現の違いはある）、(4)必要に応じた前臨床試験、(5)以上の試験で同等性／同質性が示されない場合はなんらかの非臨床試験および臨床試験を行う、というステップバイステップ、ケースバイケースの評価法である。ただし、米国 FDA は(5)を行わずして同質性／同等性の示すための方策を明確にすることをガイダンス作成の目的としている。一方、欧州は科学的立場から評価法をまとめることを目的としているようにみえるが、CPMP のガイダンスノートは臨床試験による評価を重視していながら、製造方法の変更を申請する企業にとって、恐らく最も重要である臨床試験の必要の有無に関する決定方法が曖昧にされたままである。また製造方法の変更の影響の重みづけを、製品規格と工程管理の規格値／適否の判定基準への影響に求めており、科学的な分類法とはいえない。また CPMP のガイダンスの補遺ドラフトでは、ヒトでの免疫原性試験の重視を打ち出しているが、一般原則として正しいことながら、どの程度の予測性が確保できるかは疑問である。CPMP のガイダンスの補遺ドラフトではさらに既に市販されている製品と同等であるとして後発メーカーが後発品を申請する場合（いわゆる Generic Biologicals）の同等性／同質性評価にも触れているが、同一製造メーカー内の同質性/同等性評価の延長線上の評価ととらえられており、この扱いは妥当なものと考えられる。

E．研究発表

1．口頭発表

(1) Toru KAWANISHI: Japanese Perspective, in PDA/IABs Conference “Scientific Considerations for Comparability of Biopharmaceuticals” in Prague, Feb 28, 2003

参考資料1

Guidance for Industry

Comparability Protocols — Chemistry, Manufacturing, and Controls Information

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
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http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance, HFM-40
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http://www.fda.gov/cber/guidelines.htm.
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http://www.fda.gov/cvm/guidance/published.htm

U.S. Department of Health and Human Services
Food and Drug Administration
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February 2003

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Guidance for Industry[1]

Comparability Protocols — 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 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

[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.

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.

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

[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).

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.

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

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 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]

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[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.

[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.

- Various SUPAC documents[8]

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 tests and studies that will be performed, analytical procedures that will be used, and acceptance criteria that will be achieved to assess the effect of CMC changes. A well-planned protocol provides sufficient information for FDA to determine whether the potential for an adverse effect on the product can be adequately evaluated. With a comparability protocol, the FDA can determine if a specified change can be reported in a category lower than the category for the same change, were the change to be 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, or 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. However, we recommend that each change be discrete and specific. A comparability protocol can be particularly useful for changes of a repetitive nature. We recommend that you have sufficient manufacturing information (e.g., developmental studies, manufacturing experience, demonstrated process capability, out-of-specification (OOS) investigations, stability data) with the particular product or process or similar products or processes so you can specify a priori the tests, studies, analytical procedures, and acceptance criteria appropriate for demonstrating that the CMC change or changes will not adversely affect the product. We recommend that comparability protocols be considered for CMC changes that applicants anticipate will be made.

We recommend 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 chemical, physical, microbiological, and biological properties of the product

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

- Degree to which differences in product structure and physical properties (e.g., polymorph) can be detected
- Degree of product heterogeneity if present
- The effect on safety of changes in the impurities
- The robustness of the product (i.e., the ability of product to remain unaffected by 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)

[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.

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)
- 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

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

[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).

- 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 factors relate to the safety or efficacy of the product prior to distributing product made with the change. (Section 506A(b) of the act)).

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

After a protocol is approved, you should document and submit each implemented change within the scope of the protocol using the reporting category designated by FDA. The submission would include (1) the results of all tests and studies specified in your comparability protocol, (2) discussions of any deviations that occurred during the tests or studies, (3) a summary of any investigations performed, and (4) any other pertinent information. To ensure prompt and accurate review, we recommend that you indicate in the cover letter to 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 tests and 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, you should 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 these factors 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

you review the tests, studies, analytical procedures, and acceptance criteria in your approved comparability protocol to ensure they remain current and consistent with the approved application and current FDA policy. We recommend 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. If you find the comparability protocol is no longer correct or adequate, the current protocol should be modified or withdrawn. FDA can request additional information to support a change that is implemented using an obsolete protocol.

E. How is an Approved Comparability Protocol Modified?

You can submit a revised protocol at anytime. Like an original protocol, a revised protocol should be submitted as a PAS to your application following the recommended submission 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

[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.

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.

2. Specific Tests and Studies to Be Performed

A list should be included 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) 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. Include the rationale for selecting the particular battery of tests and studies. For example, the use of nonroutine studies (e.g., characterization) can be warranted in cases where in-process or release specifications are not sufficiently discriminatory to evaluate the change.

A protocol should include a plan 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. The protocol should 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. Retained samples of prechange material can be used for comparison, provided there is no significant change in material on storage (e.g., level of degradants increasing over time). A plan would specify whether retained samples are going to be used and the maximum age of the retained samples, and include information to support the appropriateness of the use of retained samples. In general, the results from postchange material should fall within the normal batch-to-batch variation observed for prechange material.

A comparability protocol should include a plan for the stability studies that will be performed to demonstrate the equivalence of pre- and postchange product. The comparability protocol would 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. The amount of stability data that will be generated before the product made with the change is distributed would be specified. 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 from stability studies in an AR can be sufficient. If no stability studies are planned, we recommend that this be stated clearly.

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) would be described. We recommend you identify the location in your application of any referenced tests or studies.

3. Analytical Procedures to be Used

A protocol should specify the analytical procedures that you intend to use to assess the effect of the CMC changes on the product or intermediate material. Analytical procedures would be chosen capable of detecting new impurities or other changes in a product that can result from the change.

Since the current approved analytical procedures are optimized for the approved product and process, modified or new procedures may be warranted. For example, revised or new analytical procedures can be called for to monitor the removal of a new process impurity generated by a new manufacturing process. In this situation, submission of results for pre- and postchange products using both the old and new analytical procedures may be warranted. Studies performed 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 V.A.5). Validation of new modified analytical procedures or revalidation of existing analytical procedures should be performed, as appropriate. The protocol would specify that any new or revised analytical procedures and the appropriate validation or revalidation information would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.

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., X-ray crystallography, plume geometry for metered dose inhalers). If these analytical procedures are not routinely used for process or release testing, you do not have to report changes in these analytical procedures (e.g., when they are used only for drug development). However, if these analytical procedures are specified in and provided as part of a comparability protocol, any new or revised analytical procedures and, as appropriate, results from validation or qualification studies for any modified procedure would be provided when a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.

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

4. Acceptance Criteria

You should include the acceptance criteria (numerical limits, ranges or other criteria) for each specified test and study that will be used to assess the effect of the CMC changes on the product or other material and/or demonstrate equivalence between pre- and postchange material. In general, the drug substance and drug product specification would be identical to that in the approved application. Any statistical analyses that will be performed and the associated evaluation criteria would be identified.

If implementing a change using a comparability protocol calls for a revision of the drug product or drug substance specification, we recommend you consider the recommended reporting category[13] 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), the change would be reported as recommended for the specification change. 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 a postapproval CMC change implemented using the approved comparability protocol is reported to FDA.

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

You should identify the type (e.g., release, long-term or accelerated stability data) and amount of data (e.g., 3-months accelerated stability data) that will be submitted at the time a postapproval CMC change implemented using the approved comparability protocol is reported to FDA 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, 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.

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

436 *6. Proposed Reporting Category*
437
438 The use of an approved comparability protocol may justify a reduction in the reporting category for the
439 particular CMC change when implemented (see III.A). We recommend you include a proposal for the
440 reporting category that you would use for changes implemented using the approved comparability
441 protocol. FDA will evaluate your proposed reporting category as part of its review of the comparability
442 protocol and communicate any concerns about your proposal. Agreement by the applicant and FDA
443 on the reporting category for the specified CMC changes will be part of the process of approving the
444 comparability protocol.
445
446 *7. Equivalence Not Demonstrated Using the Approved Comparability Protocol*
447
448 It is anticipated that some changes in the manufacturing process will result in a postchange product that
449 cannot be demonstrated to be equivalent to the prechange product without more extensive
450 physicochemical, biological, pharmacology, PK/PD, efficacy, or safety testing or in a product that does
451 not meet the prespecified acceptance criteria in the protocol. You should identify in the protocol the
452 steps you will take in such circumstances.
453
454 *8. Commitment*
455
456 You should include a commitment in your comparability protocol that you will update or withdraw your
457 protocol when it becomes obsolete (see section IV.D)
458
459 **B. Does FDA Have Specific Concerns About Changes in the Manufacturing**
460 **Process That Should Be Addressed in a Comparability Protocol?**
461
462 In addition to the general considerations provided in section V.A, we recommend that you consider the
463 following issues for changes in the manufacturing process, where applicable:
464
465 *1. Comparison of Physical Characteristics*
466
467 A comparability protocol would normally include a plan to compare the physical characteristics (e.g.,
468 polymorph forms, particle size distribution) of the product produced using the old and new processes
469 when these characteristics are relevant to the safety and/or efficacy of the product.
470
471 *2. Comparison of Impurity Profiles*
472
473 A comparability protocol would include a plan to determine the impurity profile of the product produced
474 using the new process. The studies would assess product-related impurities and process-related
475 impurities, including, if applicable in-process reagents and catalysts. We recommend that attention be
476 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.

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

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

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

A comparability protocol for changing an analytical procedure would provide the plan for validation of the changed analytical procedure and indicate whether the protocol will be used to modify the existing analytical procedure (i.e., retaining the same principle), or to change from one analytical procedure to another (e.g., normal to reverse phase HPLC). The comparability protocol would be designed to demonstrate that the proposed changes in the analytical procedures improve or do not significantly change characteristics used in methods validation that are relevant to the type of analytical procedure (e.g., accuracy, precision, specificity, detection limit, quantitation limit, linearity, range).[14]

[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*.