U.S. Food and Drug Administration
Center for Drug Evaluation and Research

FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

Center for Biologics Evaluation and Research (CBER)

Center for Drug Evaluation and Research (CDER)

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I. Introduction

FDA is issuing this guidance document as part of its on-going initiatives to provide manufacturers with increased flexibility to bring important and improved human biological products to market more efficiently and expeditiously. This document addresses the concept of product comparability and describes current FDA practice concerning product comparability of human biological products regulated by the Center for Biologics Evaluation and Research (CBER), including therapeutic biotechnology-derived products, regulated by CBER, and therapeutic biotechnology-derived products regulated by the Center for Drug Evaluation and Research (CDER). It describes those steps that manufacturers may perform and which FDA may evaluate to allow manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy.

As with other guidance documents FDA does not intend this document to be all inclusive. It is intended to provide information and does not set forth requirements. Manufacturers may follow the procedures outlined in this document or may choose to use alternative procedures that are not provided in this document. Prior to using alternative procedures a manufacturer may wish to discuss the matter with FDA to prevent expenditure of resources generating data that FDA may later determine to be unacceptable.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency's current thinking on demonstration of product comparability. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

II. Background

Historically, biological products have been complex mixtures of molecular species that were difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that had the potential to affect many of its characteristics. In other cases, the source materials had the potential for transmitting infectious agents. Because of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a biological product was often defined by its manufacturing process. The manufacturing process for a biological product encompassed manufacturing methods, equipment, and facilities, and was a reason for the current establishment license application (ELA) requirement for biologics. FDA recognized that changes in the manufacturing process, equipment or facilities could result in

changes in the biological product itself and sometimes required additional clinical studies to demonstrate the product's safety, identity, purity and potency.

Improvements in production methods, process and control test methods, and test methods for product characterization have led to the evolution of the regulation of biological products. For example, when a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study, it may not be necessary for the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent. A sponsor may be able to demonstrate product comparability between a biological product made after a manufacturing change and a product made before implementation of the change through different types of analytical and functional testing, with or without preclinical animal testing, described in this document. FDA may determine that two products are comparable if the results of the comparability testing demonstrate that the manufacturing change does not affect safety, identity, purity, or potency.

FDA recognizes that a manufacturer may seek to make changes in the manufacturing process used to make a particular product for a variety of reasons, including improvement of product quality, yield, and manufacturing efficiency. FDA has examined proposed manufacturing changes on a case-by-case basis to determine the type of data, including clinical data, that were necessary to determine product comparability. FDA's evaluations were based, in part, upon the type of manufacturing change and the type of biological product involved. In 1990, in the "Cytokine and Growth Factor Pre-Pivotal Trial Information Package," FDA stated that "significant changes in the manufacturing process...between the time of pivotal clinical studies and submission of the PLA may result in the need to conduct additional validation, animal and *in vitro* studies, and/or clinical studies". In the 1994 " Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use," FDA included a section entitled "Issues Related to Manufacturing Changes (Demonstration of Product Equivalence)." In discussing manufacturing changes during clinical development in this document, FDA acknowledged that such changes were frequent. FDA stated that "depending on the type of *in vitro* assays and animal studies and quality of the data, extensive clinical data demonstrating equivalence may not be necessary." Manufacturers were expected to document all manufacturing changes made during development so that the procedures and manufacturing changes used in the pivotal clinical trials could be validated and the relationship to the marketed product used in earlier trials could be determined.

In the past, FDA has approved manufacturing changes made during or after completion of clinical studies in situations where comparability data have provided assurance that the product would continue to be safe, pure, and potent (effective). Such manufacturing process changes, implemented before or after product approval, have included changes implemented during the expansion from pilot scale to full scale production, the move of production facilities from one legal entity to another legal entity, and the implementation of changes in different stages of the

manufacturing process such as fermentation, purification, and formulation. In each case, FDA reviewers have used their collective scientific and regulatory experience to provide the best evaluation consistent with the applicable regulatory scheme and current knowledge.

For manufacturing changes prior to product approval, FDA interprets the phrase, "data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency," in 21 CFR 601.2(a) to include clinical data generated from a precursor product, made prior to a manufacturing change, so that the manufacturer can demonstrate that the precursor product is comparable to the manufactured product. Therefore, a manufacturer may demonstrate comparability between a product made before a manufacturing change and a product made after a manufacturing change. If a manufacturer is able, in FDA's judgement, to demonstrate comparability, FDA may permit the manufacturer to implement the changes without conducting an additional clinical trial(s) to demonstrate efficacy.

FDA recognizes that improvements in production methods, process and control test methods, and test methods for product characterization have allowed manufacturers of biological products to

readily identify and assess the impact of changes made to production processes and production facilities. For example, techniques for isolation of macromolecules, product and process related, have improved greatly in recent years. The manufacturer's ability to establish sensitive and validated assays for characterizing the product and biological activity and to evaluate the significance of differences noted in such assays can provide the basis for FDA to assess product comparability without the necessity of repeating clinical efficacy studies.

FDA has reviewed its existing guidance documents in order to clarify inconsistency or ambiguity that could potentially arise from this document and existing guidance. FDA has not found past guidance that it considers inconsistent with the guidance set forth here. However, to the extent that there is any prior guidance from FDA that is interpreted by manufacturers or others as inconsistent with this document, such guidance is superseded. To the extent that a manufacturer may have found or interpreted previous guidance to be ambiguous concerning the issue of manufacturing changes, FDA now clarifies that the comparability guidance described in this document and currently employed by FDA is FDA's operative policy for these products. See, e.g., 1983 Interferon Test Procedures: Points to Consider in the Production and Testing of Interferon Intended for Investigational Use in Humans; 1990 Cytokine Pre-Pivotal Trial Information Package (including reference that a product used in a pivotal clinical trial should be manufactured in a manner which is essentially identical to the manufacturing process that the manufacturer intends to use after approval); and 1995 FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (including reference that certain aspects of pilot production should be identical to those applied to a full commercial scale).

III. Product Comparability Testing

This document addresses comparability testing for manufacturing changes made prior to product approval and after product approval. For manufacturing changes prior to product approval, under currently applicable laws and regulations, the manufacturer must fully describe the change in any license application or investigational new drug application (IND). FDA urges manufacturers to consult with FDA prior to implementing changes that may result in comparability testing, in order to avoid delay in the review of applications.

Manufacturing changes may result in no observed alteration in a product. Alternatively, a minor alteration in one or more product characteristics, with no previously documented effect, can have either no effect or a substantial effect on the pharmacology of the product. Likewise, a major alteration in one or more product characteristics with no documented effects on the pharmacology of the product, can have either no effect or a substantial effect on the pharmacology of the product. The most important factor to FDA as it assesses product comparability is whether it is anticipated that any of any of these manufacturing changes will translate into significant changes in clinical safety or efficacy.

Manufacturers should carefully assess manufacturing changes and evaluate the product resulting from these changes for comparability to the pre-existing product. Determinations of product comparability may be based on chemical, physical, and biological assays and, in some cases, other non-clinical data. If a sponsor can demonstrate comparability, additional clinical safety and/or efficacy trials with the new product will generally not be needed. FDA will determine if comparability data are sufficient to demonstrate that an additional clinical study(ies) is unnecessary.

Knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program. In determining the types of tests needed, FDA may consider the extent of the manufacturing change(s) and the stage of manufacturing at which the change(s) occurs. Comparability testing programs may include a combination of analytical testing, biological assays (*in vitro* or *in vivo*), assessment of

pharmacokinetics and/or pharmacodynamics and toxicity in animals, and clinical testing (clinical pharmacology, safety, efficacy), with the usual progression of complexity from analytical to animal studies to human pharmacokinetics and/or pharmacodynamics to clinical safety and efficacy studies. However, comparability testing is not simply a hierarchical system in which a particular test result necessitates the next level of testing. In fact sometimes many of the tests performed are complementary. For example, analysis of the pharmacokinetics profile often suggests biological events not reflected in other types of analyses, e.g., *in vitro* assays.

Manufacturers should provide to FDA extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. When available, fully characterized reference standards for drug substance and final container material should also be used. Tests should include those routinely used for release of the bulk drug substance and final drug product in addition to tests specifically directed at fully evaluating the impact of the change on the product. Additional testing usually includes in-process assays at the manufacturing step(s) which are most likely affected by the manufacturing change(s).

Manufacturers may use the following categories of tests:

A. Analytical Testing

Analytical testing includes both chemical and physical assays. Tests should be selected which are sensitive to the full range of differences which might result from the process change. The sensitivity and breadth of analytical testing is an important determinant of the nature and extent of additional testing which should be done. These tests should include tests routinely done on all production lots, those initially used to fully characterize product structure and identity and establish product consistency from one production lot to another, and new tests if applicable.

B. Bioassays

Bioassays are functional tests which sponsors should use to assess the activity/potency of the product. These tests may also serve as measurements of the biological integrity (e.g., correct conformation) of the product and thus complement other analytical measurements. Sponsors should validate these assays and have a specific range of acceptable values for defining product activity. They may include appropriate *in vitro* tests (e.g. cell growth, enzymatic activity, anti- viral assays, infectivity assays) or *in vivo* tests in relevant animal models. If the *in vivo* mechanism of action of the product is known, the bioassay (when possible) should reflect this activity. Consideration should be given to *in vivo* and/or *in vitro* models as predictors of the biological effects in humans. For example, with vaccines, sponsors should evaluate the degree of correlation of the test(s) performed (e.g., assessment of immunogenicity) with clinical protection and submit such information to FDA so that it may be determined if a clinical study should be conducted following manufacturing changes. In cases where a product has multiple activities which are not completely correlated or the mechanism of action for clinical usage is unknown, manufacturers may need to consider performing more than one functional assay. When a drug substance has more than one form and a manufacturing change shifts the distribution of forms, determination of the bioactivity of the various forms may be of value in assessing the impact of the change.

The combined precision of the analytical and functional tests and their ability to assess significant aspects of the product are important. Both sponsors and FDA should evaluate data from both types of testing modalities to determine the extent of additional tests needed.

C. Preclinical Animal Studies

In addition to the various *in vitro* studies, *in vivo* studies in animals may be used in comparability

evaluations to determine pharmacokinetics parameters, pharmacodynamic activity, or toxicity endpoints. Animal pharmacokinetics data may be needed to assess comparability even in the absence of demonstrated differences in the analytical testing or the functional assays for the product. This is because analytical testing may be insensitive to changes affecting pharmacokinetics, and *in vitro* functional tests may not reflect the time-dependent aspects of distribution. Differences in *in vivo* exposure originating from differences in pharmacokinetics may lead to differences in therapeutic activity. Therefore, assessment of pharmacokinetics is often considered complementary to the functional assay. For hormones however, *in vivo* potency assays often take into account potential pharmacodynamics and pharmacokinetics profiles in animals. For these hormone products, when bioavailability is in question, clinical pharmacology studies may be needed to demonstrate comparability.

Adequate pharmacokinetics measurements may include determination of Cmax, Tmax, AUC and t ½ in either parallel or cross-over study designs. In cases where complications may arise from immune responses to heterologous proteins, cross-over design may be inappropriate. In other cases, sponsors should consider complicating factors related to binding proteins and levels of endogenous protein. In cases where animal studies may not be relevant, clinical pharmacology studies may be needed to show comparability.

Prior to product approval, manufacturers generally should not need to repeat all toxicology studies that were performed with the product manufactured by the previous manufacturing process in order to demonstrate product comparability. In some cases, additional animal studies may only be needed if immunogenicity is the major safety concern. The necessity and extent of additional toxicity studies may depend upon the safety profile of the pre-existing product and on the magnitude of the manufacturing process change and/or effect on the product. Situations in which additional studies may be needed include those where the product has a narrow therapeutic range or where specific safety concerns are present, e.g., when the manufacturing process change raises concerns about possible toxic impurities or adventitious agents which cannot be assessed by analytical testing.

D. Clinical Studies

Clinical studies include human pharmacology studies, immunogenicity, safety, and/or efficacy trials. Although comparability testing can include some form of clinical efficacy studies, usually one of the purposes of comparability testing, not including efficacy studies, is so FDA may determine on the basis of such comparability data that additional clinical efficacy studies, of a sufficiency to support initial licensure or approval, are unnecessary. Human pharmacology studies, generally, may be needed to evaluate changes which may affect product pharmacokinetics or pharmacodynamics, e.g., change in product formulation.

In cases where a manufacturing change(s) results in a product with structural and/or bioactivity differences, and/or differences in pharmacokinetics patterns, and those differences are meaningful with respect to potential impact on the product's safety, purity, or potency (efficacy), an additional clinical study(ies) usually may be needed to evaluate the product's safety and/or efficacy. Additionally, when the analytical and other preclinical testing is not sufficiently sensitive or broad enough to detect such meaningful differences, additional clinical study(ies) may be needed.

E. Additional considerations

In terms of comparability testing, manufacturers should generally perform extensive analytical testing complemented by functional testing if manufacturing changes occur in the process of producing the bulk drug substance. Examples of such changes include the following: a change in manufacturing site; modifications to cell or seed strains, including changes to the master cell bank; fermentation; and isolation or purification. In some cases, complementary pharmacology data or

biologic response data (e.g., antibody titers for vaccines) may be needed.

Changes made to the final drug product, such as changes in storage containers, dosage forms (e.g. from a solution to lyophilized powder for reconstitution), or filling sites, may only need comparative data on final release specifications and product stability data. However, changes in the final product formulation may need comparative pharmacokinetics studies or other types of studies.

Since each manufacturing change and each product may present unique safety, identity, purity, and potency concerns, manufacturers should consider the type of manufacturing change, stage of product development, and clinical characteristics (i.e., patient population, clinical endpoints, dosing route, steepness of the dose response curve, regimen, and duration) in any comparability testing program. In-process and final product testing should focus on the manufacturing steps affected by the process change. Manufacturers should validate the modified manufacturing process and provide data on qualification lots. The appropriate process validation criteria will vary depending on the nature of the change. The ability of the manufacturer to use validated and sensitive assays to demonstrate a product's identity and structure, biological activity and clinical pharmacology provide a basis for determining whether product comparability can be established without repeating clinical efficacy studies.

IV. Documentation of Product Comparability

This document on comparability describes testing that may be used by applicants with pending applications, licensed or approved applicants, IND sponsors, and FDA to determine the types of data that may be necessary to document product safety, purity, potency/effectiveness. FDA will determine the extent to which different types of comparability testing are necessary. For

example, in some cases FDA may determine that no clinical study(ies) is necessary. In other instances FDA may determine, on the basis of comparability data, that a clinical efficacy study(ies) is necessary.

In the interest of efficient review and approval of product applications, FDA encourages sponsors of unapproved applications or products under IND to consult with FDA regarding proposed manufacturing changes before implementing such changes prior to product approval. A sponsor may provide FDA with information regarding a manufacturing change by including a description of the change, a description of corresponding comparability tests conducted, and the comparability test data and validation information in license/ new drug applications, INDs, or amendments to pending license/ new drug applications and INDs in effect. For biological products that FDA has approved, an applicant should submit information about manufacturing changes pursuant to 21 CFR § 601.12 or 21 CFR § 314.70(g), and any FDA guidance on changes to be reported.

21 CFR § 601.12 prescribes which changes must be reported to FDA and which changes require prior approval. FDA has proposed amendments to this regulation. Manufacturers should consult the current regulation and any applicable guidance to determine the need and mechanism of reporting.

In each instance, adequate information should be available in order that FDA reviewers and investigators may understand the type of change made, the stage of production at which the change was made, and the product(s) affected. Such information should include appropriate validation of non-clinical studies and clinical studies which may vary for different products and for the manufacturing stage at which the change is implemented.

V. Conclusion

FDA may determine that manufacturers of biological products, including therapeutic biotechnology-derived products regulated as biologics or drugs, may make manufacturing changes without conducting additional clinical efficacy studies if comparability test data demonstrate to FDA that the product after the manufacturing change is safe, pure, potent/ effective.

VI. References

1. Points to Consider in the Production and Testing of Interferon Intended for Investigational Used in Humans (1983).
2. Cytokine and Growth Factor Pre-Pivotal Information Package (1990).
3. Changes to Be Reported for Product and Establishment License Applications; Guidance (April 6, 1995; 60 FR 17535).
4. FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products (July 11, 1995; 60 FR 35750)
5. Changes to an Approved Application; Proposed Rule (January, 1996; 61 FR 2739).

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