Guidance for Industry

Submission of Summary Bioequivalence Data for ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2011
Generics

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I. INTRODUCTION

This guidance is intended to assist applicants who are submitting abbreviated new drug applications (ANDAs) in complying with FDA's requirements for the submission of bioequivalence (BE) data. FDA's final rule on "Requirements for Submission of Bioequivalence Data" (the BE data rule) requires an ANDA applicant to submit data from **all** BE studies the applicant conducts on a drug product formulation submitted for approval, including studies that do not demonstrate that the generic product meets the current bioequivalence criteria.[2] All BE studies conducted on the same drug product formulation must be submitted to the Agency as either a complete study report or a summary report of the BE data.[3] The amended regulations include a definition of *same drug product formulation* (section 320.1(g)).

This guidance provides information on the following subjects:

- Types of ANDA submissions covered by the BE data rule.
- Recommended format for summary reports of BE studies.
- Types of formulations the Agency considers to be the same drug product formulation for different dosage forms based on differences in composition.

This guidance does not address which formulations the Agency considers to be the same drug product formulation based on differences in methods of manufacture.

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[1] This guidance has been prepared by the Division of Bioequivalence, Office of Generic Drugs, Office of Pharmaceutical Science, in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See the final rule, "Requirements for Submission of Bioequivalence Data," that was published in the *Federal Register* on January 16, 2009.

[3] The BE data rule amended the Agency's bioequivalence regulations in 21 CFR parts 314 and 320.

The guidance is applicable to BE studies conducted for ANDAs during both preapproval and postapproval periods.

FDA's 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

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA regulations require that an ANDA applicant submit, among other things, information showing that the applicant's drug product is bioequivalent to the approved product designated by FDA as the reference listed drug (RLD) (section 505(j)(2)(A)(iv) of the FD&C Act (21 U.S.C. 355(j)(2)(A)(iv); sections 314.94(a)(7) and 320.21(b)(1)). In the past, ANDA applicants submitted only the BE studies that demonstrated that a generic product met BE criteria,[4] but they did not typically submit additional BE studies conducted on the same drug product formulation, including studies that did not show the product met bioequivalence criteria.

The BE data rule amended FDA's regulations to require that an ANDA applicant submit data from all BE studies the applicant conducts on the drug product formulation submitted for approval (sections 314.81(b)(2)(vi), 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)). We believe that data from any additional BE studies may be important in our determination of whether a product is bioequivalent to the RLD and are relevant to our evaluation of generic products in general.[5] These data will increase our understanding of generic drug development and how changes in components and composition may affect formulation performance, as well as promote further development of science-based bioequivalence policies.

III. SUBMISSION OF ALL BIOEQUIVALENCE STUDIES

FDA regulations, as amended by and clarified in the BE data rule, require that a complete report be submitted for the BE studies upon which the applicant relies for approval and either a complete or summary report be submitted for each additional study conducted on the same drug product formulation (sections 314.81(b)(2)(vi), 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)). This requirement includes both in vivo and in vitro testing conducted to demonstrate bioequivalence. The regulations also provide that, if a summary report is submitted—and the Agency believes that there may be bioequivalence issues or concerns with the drug product—the Agency may request that a complete report be prepared and submitted to FDA.

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[4] Currently 90 percent confidence interval limits of 80 to 125.

[5] This view was endorsed by FDA's Advisory Committee for Pharmaceutical Science at a meeting held on November 16, 2000. See 68 FR 61640 at 61647, October 29, 2003.

A. What Types of ANDA Submissions Must Include All BE Studies?

Under the BE data rule, ANDA applicants are required to submit information from all BE studies conducted on the same formulation of the drug product contained in the following submissions:

- ANDAs (section 314.94).
- ANDA amendments (section 314.96(a)).
- ANDA supplements that require BE studies under section 320.21(c).
- ANDAs submitted under a suitability petition (section 314.93).
- ANDA annual reports (section 314.81(b)(2)(vi)).

B. What Format Should Be Used for a Summary Report?

For a suggested format for summary reports, go online to FDA's Generic Drugs: Information for Industry web page. The Division of Bioequivalence has developed model data summary tables in a concise format consistent with a common technical document (CTD) formatted application. The tables are located under the heading "Generic Drug Development, Abbreviated New Drug Application (ANDA) Submissions, and Review Information." The Agency recommends that these table formats be used to organize the data for summary reports required by the BE data rule.

IV. SAME DRUG PRODUCT FORMULATION

FDA amended the regulations to require an applicant to submit data from all BE studies conducted on the same formulation of the drug product submitted for approval. In section 320.1(g), FDA added a definition of the term *same drug product formulation*:

> *Same drug product formulation* means the formulation of the drug product submitted for approval and any formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the FDA's determination of bioequivalence.

The definition of *same drug product formulation* in section 320.1(g) applies regardless of whether the products are manufactured at the same or different manufacturing sites.[6]

In the following sections, we discuss differences in composition to consider when comparing drug product formulations. For immediate-release (IR) and extended-release (ER) drug products, we discuss:

- Minor differences in composition that are unlikely to have any detectable impact on formulation quality and performance between the formulations being compared. These

[6] See the preamble of the BE data rule, FDA response to comment 15.

differences would result in formulations that meet the definition of *same drug product formulation* and for which BE studies must be submitted (sections 314.81(b)(2)(vi), 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)).

- Differences in composition that are likely to result in a significant difference in formulation quality and performance between the formulations being compared. These differences would result in formulations that do not meet the definition of *same drug product formulation* and for which BE studies need not be submitted.

A. Immediate-Release Drug Products

1. Immediate-Release Formulations Considered to Be the Same

Minor differences that result in product formulations that are considered to be the same include the following:

- A difference in an ingredient intended to affect the color or flavor of the drug product.
- A different approved ingredient of the printing ink.
- A difference in the technical grade and/or specification of an excipient (e.g., Avicel PH102 versus Avicel PH200).
- A difference in particle size of the drug substance or excipients.

Formulations with different amounts of excipients are considered to be the same drug product formulation if:

- For an individual excipient, the difference in weight between the formulations being compared is less than or equal to the percentage shown in Table 1, and
- The cumulative total of all excipient weight differences is less than or equal to 10 percent.

Table 1. Immediate-Release Formulations—Differences in Excipient Weights

Excipient	Difference (≤) in Excipient Weights Between Two Formulations*
Filler	10
Disintegrant	
Starch	6
Other	2
Binder	3
Lubricant	
Calcium or Magnesium Stearate	0.5
Other	2
Glidant	
Talc	2
Other	0.2
Film Coat	2

* Percentage of difference between the formulation proposed for marketing and another experimental formulation.

Illustrative examples of IR formulations considered to be the same are provided below:

- If the amount of a filler excipient in an experimental formulation (A) is 105 mg and the same filler excipient in the formulation proposed to be marketed (B) is 100 mg, the difference in the excipient weight is 5 percent. These two formulations would be considered the same because the difference in weight of the filler excipient is less than 10 percent.

- In the case of multiple excipient changes, if an experimental formulation (A) contains 95 mg of a filler excipient and 103 mg of a disintegrant and the formulation proposed for marketing (B) contains 100 mg of the same filler excipient and 100 mg of the same disintegrant, the difference in weight for the filler excipient is 5 percent and the difference in weight for the disintegrant is 3 percent. The cumulative change is 8 percent, which is less than 10 percent for all excipient differences. Therefore, these formulations would be considered the same.

2. Immediate-Release Formuations Considered Not to Be the Same

A difference that results in product formulations that are considered not to be the same would include the addition or deletion of an excipient (with the exception of a difference in an ingredient intended to affect the color or flavor of the drug product or a difference in an ingredient of the printing ink).

Formulations with different amounts of the same excipients are considered not to be the same drug product formulation if:

- For an individual excipient, the difference in excipient weight between the formulations being compared exceeds the percentages shown in Table 1, or

- The cumulative total of all excipient weight differences exceeds 10 percent.

Illustrative examples of IR formulations considered not to be the same are provided below:

- If the amount of a filler excipient in an experimental formulation (A) is 115 mg and the filler excipient in the formulation proposed for marketing (B) is 100 mg, the difference in the excipient weight would be 15 percent. These two formulations would not be considered the same because the difference in weight of the filler excipient is greater than 10 percent.

- In the case of multiple excipient changes, if an experimental formulation (A) contains 90 mg of a filler excipient and 106 mg of a disintegrant and the formulation proposed for marketing (B) contains 100 mg of the filler excipient and 100 mg of the disintegrant, the difference in weight for the excipient is 10 percent and the difference in weight for the disintegrant is 6 percent. The cumulative change would be 16 percent. Therefore, these formulations would not be considered the same, and any studies conducted with formulation A would not need to be submitted.

3. *Immediate Release Formulations - Other*

Studies performed on experimental formulations containing different polymorphic forms of the drug substance also should be submitted.

B. Extended-Release Drug Products—Nonrelease Controlling Excipients

1. Extended-Release Formulations Considered to Be the Same (Nonrelease Controlling Excipients)

Minor differences that result in product formulations that are considered to be the same include the following:

- A difference in an ingredient intended to affect the color or flavor of the drug product.

- A different approved ingredient of the printing ink.

- A difference in the technical grade and/or specification of a nonrelease controlling excipient (e.g., Avicel PH102 versus Avicel PH200).

- A difference in particle size of the drug substance or excipients.

Formulations with different amounts of the same nonrelease controlling excipients are considered to be the same drug product formulation if:

- For an individual excipient, the difference in excipient weight between the formulations being compared is less than or equal to the percentages listed in Table 2, and

- The cumulative total of all excipient weight differences is less than or equal to 10 percent.

Table 2. Extended-Release Formulations—Differences in Excipient Weights

Nonrelease Controlling Excipient	Difference (≤) in Excipient Weights Between Two Formulations*
Filler	10
Disintegrant	
Starch	6
Other	2
Binder	1
Lubricant	
Calcium or Magnesium Stearate	0.5
Other	2
Glidant	
Talc	2
Other	0.2
Film Coat	2

*Percentage of difference between the formulation proposed for marketing and another experimental formulation.

2. Extended-Release Formulations Considered Not to Be the Same (Nonrelease Controlling Excipients)

Examples of differences that result in product formulations that are considered not to be the same include the following:

- The addition or deletion of an excipient (except for a difference in an ingredient intended to affect the color or flavor of the drug product or a difference in an ingredient of the printing ink).

- A difference in weight of a nonrelease controlling excipient between the formulations being compared that exceeds the percentage listed in Table 2.

- The cumulative total difference in weights of all nonrelease controlling excipients exceeds 10 percent.

3. *Extended Release Formulations – Other (Nonrelease Controlling Excipients)*

Studies performed on experimental formulations containing different polymorphic forms of the drug substance also should be submitted.

C. Extended-Release Drug Products—Release Controlling Excipients

1. Extended-Release Formulations Considered to Be the Same (Release Controlling Excipients)

Examples of minor differences that result in product formulations that are considered to be the same include the following:

- A difference in the technical grade and/or specification of the release controlling excipient(s) (e.g., Eudragit RS 100 versus Eudragit RL 100).
- A difference in particle size of the drug substance or excipients.
- A difference in the amount of release controlling excipient(s), expressed as the difference in weight of the release controlling excipient(s) in the experimental formulation compared to the formulation proposed for marketing, of less than or equal to 10 percent.

2. Extended-Release Formulations Considered Not to Be the Same (Release Controlling Excipients)

Examples of differences that result in product formulations that are considered not to be the same include the following:

- The addition or deletion of a release controlling excipient.
- A difference in the amount of release controlling excipient(s), expressed as the difference in weight of the release controlling excipient(s) in the experimental formulation compared to the formulation proposed for marketing, of greater than 10 percent.

3. *Extended Release Formulations – Other (Release Controlling Excipients)*

Studies performed on experimental formulations containing different polymorphic forms of the drug substance also should be submitted.

D. Semisolid Dosage Forms

For the purposes of this guidance, formulations of semisolid dosage form products are considered to be the same if the experimental formulation is in the same category as the formulation proposed for marketing (e.g., the formulations being compared are both for creams) and any differences between formulations are as described below.

- If the difference in the amount of an individual excipient between the experimental formulation and the formulation intended to be marketed is less than or equal to 5 percent, the two formulations are considered to be the same.

- If more than one excipient amount is changed, and the cumulative total of differences in the amount of all excipients is less than or equal to 7 percent, the two formulations are considered to be the same.

- Formulations with differences in particle size distribution of the drug substance, if the drug is in suspension, are considered to be the same.

Formulations with differences in technical grade of a structure forming excipient are considered not to be the same.

E. Other Complex Dosage Forms

For other complex dosage forms (e.g., transdermals, injectable suspensions, and suppositories), limited information is available regarding quantitative and qualitative changes that could have a significant impact on the bioavailability of the product. Because of this lack of information, we consider all experimental formulations that are pharmaceutically equivalent to the formulation of the complex dosage form product intended to be marketed to be the same as the RLD. Therefore, the Agency requests submission of either a summary report or a complete report of all bioavailability or bioequivalence studies conducted during the development of the drug product. This information will increase our understanding of the development of the generic product and how changes in components, composition, and methods of manufacture have affected formulation performance. Access to this information will promote further development of science-based bioequivalence policies for complex dosage forms.