
Guidance for Industry

Submission of Summary Bioequivalence Data for ANDAs

DRAFT GUIDANCE

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

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Guidance for Industry¹

Submission of Summary Bioequivalence Data for ANDAs

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist applicants who are submitting abbreviated new drug applications (ANDAs) in complying with FDA's new requirements for the submission of bioequivalence (BE) data. FDA's final rule on "Requirements for Submission of Bioequivalence Data" (the BE data rule) requires ANDA applicants 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* (§ 320.1(g)).

This guidance provides information on the following subjects:

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

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

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

² See the final rule "Requirements for Submission of Bioequivalence Data" published in the *Federal Register* on January 16, 2009 (the BE data rule).

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

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

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

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II. BACKGROUND

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47 The Federal Food, Drug, and Cosmetic Act (the Act) and FDA regulations require that ANDA
48 applicants submit, among other things, information showing that the applicant's drug product is
49 bioequivalent to the approved product designated by FDA as the reference listed drug (RLD)
50 (section 505(j)(2)(A)(iv) of the Act (21 U.S.C. 355(j)(2)(A)(iv)); §§ 314.94(a)(7) and
51 320.21(b)(1)). In the past, ANDA applicants have submitted only the BE studies that
52 demonstrate that a generic product meets BE criteria,⁴ but have not typically submitted additional
53 BE studies conducted on the same drug product formulation, including studies that do not show
54 the product meets bioequivalence criteria.

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56 The BE data rule amended FDA's regulations to require that ANDA applicants submit data from
57 all BE studies the applicant conducts on the drug product formulation submitted for approval
58 (§§ 314.81(b)(2)(vi), 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)). The FDA believes
59 that data from any additional BE studies may be important in our determination of whether a
60 product is bioequivalent to the RLD, and are relevant to our evaluation of generic products in
61 general.⁵ These data will (1) increase our understanding of generic drug development and how
62 changes in components and composition may affect formulation performance, and (2) promote
63 further development of science-based bioequivalence policies.

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III. SUBMISSION OF ALL BIOEQUIVALENCE STUDIES

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68 FDA regulations, as amended by and clarified in the BE data rule, require that a complete report
69 be submitted for the BE studies upon which the applicant relies for approval, and either a
70 complete or summary report be submitted for each additional study conducted on the same drug
71 product formulation (§§ 314.81(b)(2)(vi), 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)).
72 This requirement includes both in vivo and in vitro testing conducted to demonstrate
73 bioequivalence. The regulations also provide that, if a summary report is submitted, and the

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.

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74 Agency believes that there may be bioequivalence issues or concerns with the drug product, the
75 Agency may request that a complete report be prepared and submitted to FDA.

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

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

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

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

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IV. SAME DRUG PRODUCT FORMULATION

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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 § 320.1(g),
FDA added a definition of the term *same drug product formulation*:

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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.

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The definition of *same drug product formulation* in § 320.1(g) applies regardless of whether the
products are manufactured at the same or different manufacturing sites.⁷

⁶ The OGD Web page address is <http://www.fda.gov/cder/ogd/index.htm>.

⁷ See the preamble of the BE data rule, FDA response to comment 15.

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

- 115 • minor differences in composition that are unlikely to have any detectable impact on
116 formulation quality and performance between the formulations being compared. These
117 differences would result in formulations that meet the definition of *same drug product*
118 *formulation*, and for which BE studies must be submitted (§§ 314.81(b)(2)(vi),
119 314.94(a)(7), 314.96(a)(i), and 320.21(b)(1) and (c)).
- 120 • differences in composition that are likely to result in a significant difference in
121 formulation quality and performance between the formulations being compared. These
122 differences would result in formulations that do not meet the definition of *same drug*
123 *product formulation*, and for which BE studies need not be submitted.

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A. Immediate-Release (IR) Drug Products

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I. IR Formulations Considered the Same

130 Minor differences that result in product formulations that are considered the same
131 include:
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- 133 • A difference in an ingredient intended to affect the color or flavor of the drug
134 product
- 135 • A different approved ingredient of the printing ink
- 136 • A difference in the technical grade and/or specification of an excipient (e.g.,
137 Avicel PH102 vs. Avicel PH200)
- 138 • A difference in particle size or polymorphic form of the drug substance or
139 excipients.

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

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

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Table 1. IR Formulations — Differences in Excipient Weights

Excipient	Difference (\leq) in Excipient Weights Between Two Formulations¹
Filler	10
Disintegrant	
Starch	6
Other	2
Binder	3
Lubricant	
Calcium (Ca) or Magnesium (Mg) Stearate	0.5
Other	2
Glidant	
Talc	2
Other	0.2
Film Coat	2

¹ Percentage of difference between the formulation proposed for marketing and another experimental formulation.

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Illustrative examples:

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- If the amount of a filler excipient in an experimental formulation (A) is 105 milligrams (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 weights of the filler excipient is less than 10 percent.

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- 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 and 100 mg of the same disintegrant, the difference in weight for the filler is 5 percent, and the difference in weight for the disintegrant is 3 percent. The cumulative change is 8 percent, less than 10 percent for all excipient differences. Therefore, these formulations would be considered the same.

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2. *IR Formulations Considered Not the Same*

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A difference that results in product formulations that are not considered 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).

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

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- 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.

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181 Illustrative examples:

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- 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 weights of the filler excipient is greater than 10 percent.

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- 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 and 100 mg of the disintegrant, the difference in weight for the filler 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.

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B. Extended-Release (ER) Drug Products — Nonrelease Controlling Excipients

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1. ER Formulations Considered the Same (Nonrelease Controlling Excipients)

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202 Minor differences that result in product formulations that are considered the same

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- 205
- 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 vs. Avicel PH200)
 - A difference in particle size or polymorphic form of the drug substance or excipients.

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213 Formulations with different amounts of the same nonrelease controlling excipients are

214 considered the same drug product formulation if:

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- 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.

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Table 2. ER Formulations — Differences in Excipient Weights

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

¹ Percentage of difference between another experimental formulation and the formulation proposed for marketing.

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2. *ER Formulations Not Considered the Same (Nonrelease Controlling Excipients)*

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

- 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.

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C. **Extended-Release (ER) Drug Products — Release Controlling Excipients**

1. *ER Formulations Considered the Same (Release Controlling Excipients)*

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

- A difference in the technical grade and/or specification of the release controlling excipient(s) (e.g., Eudragit RS 100 vs. Eudragit RL 100)

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- A difference in particle size or polymorphic form 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. *ER Formulations Not Considered the Same (Release Controlling Excipients)*

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

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- 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.

D. Semisolid Dosage Forms

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For the purposes of this guidance, formulations of semisolid dosage form products are considered 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.

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

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

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292 **E. Other Complex Dosage Forms**
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294 For other complex dosage forms (such as transdermals, injectable suspensions, and
295 suppositories), there is limited information regarding quantitative and qualitative changes
296 that could have a significant impact on the bioavailability of the product. Because of this
297 lack of information, we consider all experimental formulations that are pharmaceutically
298 equivalent to the formulation of the complex dosage form product intended to be
299 marketed to be the same as the reference listed drug. Therefore, the FDA requests
300 submission of either a summary report or a complete report of all bioavailability or
301 bioequivalence studies conducted during the development of the drug product. This
302 information will increase our understanding of the development of the generic product
303 and how changes in components, composition, and methods of manufacture have affected
304 formulation performance. Access to this information will also promote further
305 development of science-based bioequivalence policies for complex dosage forms.
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