
Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2013
Biopharmaceutics**

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Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

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**U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 provides recommendations to applicants planning to include bioequivalence (BE) information in abbreviated new drug applications (ANDAs) and ANDA supplements. The guidance describes how to meet the BE requirements set forth in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations. The guidance is generally applicable to dosage forms intended for oral administration and to non-orally administered drug products in which reliance on systemic exposure measures is suitable for documenting BE (e.g., transdermal delivery systems and certain rectal and nasal drug products). We believe that the guidance will also be useful when planning BE studies intended to be conducted during the postapproval period for certain changes in an ANDA.

This guidance revises and replaces parts of two FDA guidances for industry,² relating to BE and fed BE studies to be submitted in ANDAs. This guidance does not address bioavailability (BA), BE, and food effect studies in investigational new drug applications (INDs) and new drug applications (NDAs). A separate guidance will soon be available that will address BA and BE studies for INDs, NDAs, and NDA supplements.³ FDA has determined that separating guidances according to application type will be beneficial to applicants.

¹ This guidance was 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.

² *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations* and *Food-Effect Bioavailability and Fed Bioequivalence Studies*.

³ Many guidances are referenced throughout this document, and they can be found on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. We update guidances periodically. To make sure you have the most recent version of a guidance, check this CDER guidance Web site.

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37 In addition, FDA routinely publishes guidances on BE study design for specific products.⁴ FDA
38 recommends that applicants consult this general guidance in conjunction with any relevant
39 product-specific guidance when considering the appropriate BE study for a proposed product.
40

41 FDA's guidance documents, including this guidance, do not establish legally enforceable
42 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
43 be viewed only as recommendations, unless specific regulatory or statutory requirements are
44 cited. The use of the word *should* in Agency guidances means that something is suggested or
45 recommended, but not required.
46

47 **II. BACKGROUND**

48 To receive approval for an ANDA, an applicant generally must demonstrate, among other things,
49 that its proposed drug product is bioequivalent to the reference listed drug (RLD, or reference
50 product).⁵ The FD&C Act provides that a generic drug is bioequivalent to the listed drug if:
51
52

53 The rate and extent of absorption of the drug do not show a significant difference
54 from the rate and extent of absorption of the listed drug when administered at the
55 same molar dose of the therapeutic ingredient under similar experimental
56 conditions in either a single dose or multiple doses....⁶
57

58 For most products, the focus of BE studies is on the release of the drug substance from the drug
59 product into the systemic circulation. During such BE studies, an applicant compares the
60 systemic exposure profile of a test drug product to that of the RLD.
61

62 **III. ESTABLISHING BIOEQUIVALENCE**

63 Under FDA regulations, an applicant must use “the most accurate, sensitive, and reproducible
64 approach available among those set forth” in 21 CFR 320.24(b) to demonstrate BE.⁷ As noted in
65 21 CFR 320.24, in vivo and/or in vitro methods can be used to establish BE. In general
66 descending order of preference, these include pharmacokinetic, pharmacodynamic, clinical, and
67 in vitro studies.⁸
68
69
70

⁴ See guidance for industry on *Bioequivalence Recommendations for Specific Products* at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

⁵ See section 505(j)(2)(A)(iv) of the FD&C Act; 21 CFR 314.94(a)(7).

⁶ Section 505(j)(8)(B)(i) of the FD&C Act. See also section 505(j)(8)(B)(ii), (C) of the FD&C Act; 21 CFR 320.1(e), and 320.23(b).

⁷ See 21 CFR 320.24(a).

⁸ See 21 CFR 320.24(b).

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71 **A. Pharmacokinetic Studies**

72

73 **1. General Considerations**

74

75 As provided above, the statutory definition of BE, expressed in terms of rate and extent of
76 absorption of the active ingredient or moiety, emphasizes the use of pharmacokinetic endpoints
77 in an accessible biological matrix, such as blood, plasma, and/or serum, to indicate release of the
78 drug substance from the drug product into the systemic circulation.⁹ BE frequently relies on
79 pharmacokinetic endpoints such as C_{max} (peak plasma concentration) and AUC (area under the
80 plasma concentration time curve) that are reflective of rate and extent of absorption, respectively.

81

82 If serial measurements of the drug or its metabolites in plasma, serum, or blood cannot be
83 accomplished, measurement of urinary excretion can be used to demonstrate BE.

84

85 **2. Pilot Study**

86

87 If the applicant chooses, a pilot study in a small number of subjects can be carried out before
88 proceeding with a full BE study. This pilot study can be used to validate analytical
89 methodology, assess variability, optimize sample collection time intervals, and provide other
90 information.

91

92 **3. Pivotal Bioequivalence Studies**

93

94 General recommendations for a standard BE study based on pharmacokinetic measurements are
95 provided in the Attachment.

96

97 **4. Study Designs**

98

99 FDA recommends use of a two-period, two-sequence, two-treatment, single-dose, crossover
100 study design, a single-dose parallel study design, or a replicate study design for BE studies. For
101 most dosage forms that release drug intended to be systemically available, we recommend that
102 applicants perform a two-period, two-sequence, two-treatment, single-dose, crossover study
103 using healthy subjects. In this design, each study subject should receive each treatment (test, and
104 RLD) in random order. The crossover design may not be practical for drugs with long
105 pharmacokinetic half-lives (i.e., longer than 24 hours). In such cases, investigators can use a
106 single-dose, parallel design where each treatment should be administered to a separate group of
107 subjects with similar demographics. The general recommendations for study designs provided in
108 the Attachment should be used in designing crossover studies as well.

109

110 A replicate crossover study may be an appropriate alternative to the parallel or nonreplicate
111 crossover study described above, and can be conducted as either a partial (three-way) or full
112 (four-way) replication of treatment. In this design, one or both treatments should be
113 administered to the same subject on two separate occasions. The replicate design has the
114 advantage of using fewer subjects although each subject should receive more treatments than in

⁹ See section 505(j)(8)(B) of the FD&C Act.

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115 the two-treatment, crossover design. The replicate design is especially useful for highly variable
116 drugs.

117
118 We recommend that applicants use the average BE method of analysis with these study designs
119 for establishing BE. In limited cases, applicants may use a scaled-average BE analysis approach
120 for highly variable drugs.¹⁰ This analysis approach is typically used with a replicate study
121 design. Recommendations for replicate study designs and the average BE approach method can
122 be found in the guidance for industry on *Statistical Approaches to Establishing*
123 *Bioequivalence*.¹¹

124
125 For applicants wishing to use variations of these study designs or analysis methods (e.g., a
126 sequential design or scaled-average BE), we recommend that you submit a complete protocol for
127 review and comment before starting the study.

128 5. *Study Population*

130
131 In general, unless otherwise recommended in a specific guidance:

- 133 • Subjects recruited for in vivo BE studies should be 18 years of age or older.
- 134
135 • In vivo BE study subjects should be representative of the general population,
136 taking into account age, sex, and race.
- 137
138 • If a drug product is intended for use in both sexes, the applicant should include
139 similar proportions of males and females in the study.
- 140
141 • If the drug product is predominantly intended for use in the elderly, the applicant
142 should include as many subjects as possible at or above age 60.
- 143
144 • The total number of subjects in a study should be sufficient to provide adequate
145 statistical power for BE demonstration, but we do not expect that there will be
146 sufficient power upon which to draw conclusions for each subgroup.

147
148 In most cases, we do not recommend statistical analysis of subgroups.

149
150 We also recommend that any restrictions on admission into a study be based primarily on safety
151 considerations. Sometimes, safety considerations preclude the use of healthy volunteers. In such

¹⁰ For highly variable drugs (intrasubject variability $\geq 30\%$), applicants can conduct BE studies using a replicate design approach. Alternatively, a single-dose, randomized, three-period reference-scaled, average BE approach is also appropriate. The reference-scaled average BE approach adjusts the BE limits of highly variable drugs by scaling to the within-subject variability of the RLD in the study and imposes a limit of 0.8 to 1.25 on the geometric mean ratio. The within-subject variability of RLD should be determined using a three-way modified replicate-design study in which the RLD is given twice and the test product is given once. For general information on the reference-scaled approach, investigators should refer to the published book chapter, *Davit B, Conner D. Reference-scaled average bioequivalence approach*. In: Kanfer I, Shargel L, eds. *Generic Drug Product Development – International Regulatory Requirements for Bioequivalence*. New York, NY: Informa Healthcare, 2010:271-272.

¹¹ See footnote 3.

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152 situations, applicants should attempt to enroll patients that the drug is intended to treat and whose
153 disease process and treatments are stable for the duration of the BE study. An IND for certain
154 BE studies may be required, for example, for cytotoxic products.¹²

155

156 6. *Single-Dose Studies*

157

158 We usually recommend single-dose pharmacokinetic studies for both immediate and modified
159 release drug products to demonstrate BE because these studies are generally more sensitive than
160 steady-state studies in assessing differences in the release of the drug substance from the drug
161 product into the systemic circulation.

162

163 7. *Steady-State Studies*

164

165 When safety considerations suggest using patients who are already receiving the medication,
166 often the only way to establish BE without disrupting a patient's ongoing treatment is in a steady-
167 state study. We recommend that if a steady-state study is recommended, applicants carry out
168 appropriate dosage administration and sampling to document the attainment of steady-state.

169

170 8. *Bioanalytical Methodology*

171

172 We recommend applicants ensure that bioanalytical methods for BE studies are accurate, precise,
173 selective, sensitive, and reproducible. A separate draft guidance for industry on *Bioanalytical*
174 *Method Validation* is available to assist applicants in validating bioanalytical methods.¹³

175

176 9. *Pharmacokinetic Measures of Rate and Extent of Exposure*

177

178 a. Rate of Absorption (Peak Exposure)

179

180 For both single-dose and steady-state studies, we recommend that you assess the rate of
181 absorption by measuring the peak drug concentration (C_{\max}) obtained directly from the data
182 without interpolation. The time-to-peak drug plasma concentrations (T_{\max}) can also provide
183 important information regarding the rate of absorption.

184

185 b. Partial Exposure

186

187 For orally administered immediate release drug products, BE can generally be demonstrated by
188 measurements of peak and total exposure. We recommend the use of partial AUC as an early
189 exposure measure under certain circumstances. The time to truncate the partial area should be
190 related to a clinically relevant pharmacodynamic (PD) measure. We recommend that sufficient
191 quantifiable samples be collected to allow adequate estimation of the partial area. For further
192 information on specific products, applicants should consult our website to determine whether a
193 product-specific guidance for the proposed product is available.¹⁴

¹² See 21 CFR 312.2(c) and 320.31.

¹³ See footnote 3.

¹⁴ See footnote 3.

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c. Extent of Absorption (Total Exposure)

For single-dose studies, we recommend that the indicators for extent of absorption be both of the following:

- Area under the plasma/serum/blood concentration-time curve from time zero to time t (AUC_{0-t}), where:
 - t is the last time point with a measurable concentration.
- Area under the plasma/serum/blood concentration-time curve from time zero to time infinity (AUC_{0-inf}), where:
 - $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$
 - C_t is the last measurable drug concentration
 - λ_z is the terminal or elimination rate constant calculated according to an appropriate method.

For steady-state studies, we recommend that the indicator for extent of absorption be the area under the plasma, serum, or blood concentration-time curve over a dosing interval at steady-state (AUC_{0-tau}), where tau is the length of the dosing interval.

10. Fed Bioequivalence Studies

Co-administration of food with oral drug products can influence BE. Therefore, fed BE studies can determine whether test and RLD products are bioequivalent when co-administered with meals. We usually recommend a single-dose, two-period, two-treatment, two-sequence, crossover study for fed BE studies. See Attachment for details on study design.

When a fasting in vivo BE study is recommended for an orally administered, immediate release product, we recommend that applicants conduct a fed study, except when the *dosage and administration* section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered 1 hour before or 2 hours after a meal).

For orally administered, immediate release products labeled to be taken only with food, fasting and fed studies are recommended, except when serious adverse events are anticipated with fasting administration. In these latter cases, we recommend that applicants conduct only a fed study; a fasting study is not recommended.

For all orally administered, modified-release drug products, we recommend that applicants conduct a fed BE study in addition to a fasting BE study. These studies should usually be conducted on the highest strength of the drug product, unless safety considerations preclude the use of that dose in study subjects.

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238 11. *Sprinkle Bioequivalence Studies*

239
240 If the label of a modified release RLD product states that the product can be administered
241 sprinkled in soft foods, we recommend applicants conduct an additional BE study. For each
242 treatment arm, the product should be sprinkled on one of the soft foods mentioned in the labeling
243 of the RLD, normally applesauce. Aside from administration in the soft food, this additional
244 study should follow the recommendations for the fasting BE study described in the Appendix.
245

246 12. *Bioequivalence Studies of Products Administered in Specific Beverages*

247
248 There are certain products with labeling that specifies that the product must be administered in a
249 specific beverage. BE studies for these products should be administered mixed with one of the
250 beverages mentioned in the labeling. If additional beverages are listed, applicants should
251 provide evidence that using these additional beverages would not result in BE differences.
252

253 If there are questions about the use of other vehicles, or the design or analysis of such BE
254 studies, applicants should contact the appropriate staff in the Agency's Office of Generic Drugs
255 (OGD).
256

257 **B. General Considerations on Other Bioequivalence Studies**

258
259 In certain circumstances other BE studies are recommended to support a demonstration of BE.
260 Below are some general considerations regarding these other BE studies. Sponsors should
261 consult FDA's guidances for industry for additional information on these methods as well.¹⁵
262

263 1. *In Vitro Tests Predictive of Human In Vivo Bioavailability (In Vitro-In Vivo* 264 *Correlation Studies)*

265
266 In vitro-in vivo correlation (IVIVC) is a scientific approach to describe the relationship between
267 an in vitro attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant in
268 vivo response (e.g., plasma drug concentration or amount of drug absorbed). This model
269 relationship facilitates the rational development and evaluation of extended-release dosage forms
270 as a surrogate for bioavailability and/or BE testing, as well as a tool for formulation screening
271 and setting of the dissolution/drug release acceptance criteria.
272

273 Additional information specifically on the development and validation of an IVIVC can be found
274 in the guidance for industry on *Extended Release Oral Dosage Forms: Development, Evaluation,*
275 *and Application of In Vitro/In Vivo Correlations.*
276

277 2. *Pharmacodynamic*

278
279 A suitably validated pharmacodynamic method can be used to demonstrate BE. However, we do
280 not recommend pharmacodynamic studies for drug products that are intended to be absorbed into
281 the systemic circulation and for which a pharmacokinetic approach can be used to establish BE.
282

¹⁵ See footnote 3.

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283 3. *Comparative Clinical Studies*

284
285 When it is not possible to use the previously described methods, well-controlled BE studies with
286 clinical endpoints in patients can be used to establish BE.

287 288 4. *In Vitro Studies*

289
290 Under certain circumstances, BE can be evaluated using in vitro approaches (e.g.,
291 dissolution/drug release testing) under 21 CFR 320.24(b). FDA does not recommend in vitro
292 approaches for drug products that are intended to be systemically absorbed. Such approaches
293 would be appropriate; however, in other circumstances (e.g., for drug products that bind bile
294 acids in the gastrointestinal tract).

295 296 297 **IV. ESTABLISHING BIOEQUIVALENCE FOR DIFFERENT DOSAGE FORMS**

298
299 The following sections provide recommendations for establishing BE for specific dosage forms.
300 As explained below, in certain cases BE testing may be waived.

301 302 **A. Oral Solutions**

303
304 For oral solutions, elixirs, syrups, tinctures, or other solubilized forms, an in vivo BE testing
305 requirement may be waived for certain products on the ground that in vivo BE is self-evident. In
306 such instances, the applicant would be deemed to have complied with and fulfilled any
307 requirement for in vivo BE data.¹⁶ For example, BE can be waived for an oral solution if the
308 formulation has the same active ingredient in the same concentration and dosage form as the
309 RLD, and does not contain any excipient that significantly affects drug absorption or
310 availability.¹⁷

311 312 **B. Immediate Release Products: Capsules and Tablets**

313 314 1. *Preapproval*

315
316 For immediate release capsule and tablet products, we recommend the following studies: (1) a
317 single-dose, fasting study comparing the highest strength of the test and RLD products and (2) a
318 single-dose, fed BE study comparing the highest strength of the test and RLD products (see
319 section III.A.10).

320
321 Conducting an in vivo study on a strength other than the highest may be appropriate for reasons
322 of safety, with concurrence by the Division of Bioequivalence, OGD, if the following conditions
323 are met:

- 324
325 • Linear elimination kinetics has been documented over the therapeutic dose
326 range.

¹⁶ See 21 CFR 320.22(b)(3).

¹⁷ Ibid.

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- 327
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- 331
- The higher strengths of the test and RLD products are proportionally similar to their corresponding lower strength.
 - Comparative dissolution testing on the higher strength of the test and RLD products has been submitted and found to be acceptable.

332 An in vivo BE requirement for one or more strength(s) can be waived based on (i) acceptable BE
333 study on the designated strength, (ii) acceptable in vitro dissolution testing of all the strengths,
334 and (iii) proportional similarity of the formulations across all strengths.¹⁸

335

336 This guidance defines *proportionally similar* in the following ways:

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- 355
- All active and inactive ingredients are in similar proportion between different strengths (e.g., a tablet of 50-mg strength has all the inactive ingredients—almost exactly half that of a tablet of 100-mg strength, and almost twice that of a tablet of 25-mg strength).
 - For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low): (1) the total weight of the dosage form remains nearly the same for all strengths (within $\pm 10\%$ of the total weight of the strength on which a biostudy was performed), (2) the same inactive ingredients are used for all strengths, and (3) the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients.
 - Active and inactive ingredients that are not in similar proportion between different strengths can be considered proportionally similar with adequate justification (such as dosage form proportionality studies that demonstrate equivalent in vivo bioavailability).

356 Under any of these scenarios, we recommend that in vivo BE studies be accompanied by in vitro
357 dissolution profiles on all strengths of each product. We also recommend that applicants conduct
358 the BE study comparing the test product and the RLD using the strength(s) specified in *Approved*
359 *Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the *Orange*
360 *Book*).¹⁹

361

362 In addition, for highly soluble, highly permeable, rapidly dissolving, and orally administered
363 immediate release drug products, in vitro data may be acceptable to demonstrate BE based on the
364 biopharmaceutics classification system as described in the guidance for industry on *Waiver of In*
365 *Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage*
366 *Forms Based on a Biopharmaceutics Classification System*.²⁰

367

¹⁸ See 21 CFR 320.22(d)(2).

¹⁹ See <http://www.fda.gov/cder/orange/default.htm>.

²⁰ See footnote 3.

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368 For additional information on BE study design for a specific product, we recommend that
369 applicants consult our website to determine whether a product-specific guidance for your
370 proposed product is available.²¹

371

372 2. *Postapproval*

373

374 Please refer to the guidance for industry *Immediate Release Solid Oral Dosage Forms, Scale-Up*
375 *and Postapproval Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In*
376 *vivo Bioequivalence Documentation* for information regarding BE testing recommended for
377 specified types of postapproval changes.²²

378

379 For postapproval changes, we recommend that applicants make the in vitro comparison between
380 the prechange and postchange products. When in vivo BE studies are recommended to support a
381 postapproval change for an ANDA product, FDA recommends that applicants compare the
382 postchange ANDA drug product to the RLD and not to the prechange ANDA product.

383

384 **C. Suspensions**

385

386 We generally recommend that you establish BE for a suspension in the same manner as for other
387 solid oral dosage forms. In vivo studies and dissolution testing should be performed as described
388 in section B (above) on immediate release products, or in section D (below) on modified release
389 products.

390

391 **D. Modified Release Products**

392

393 Modified release products include delayed release products and extended release (controlled
394 release or sustained release) products.

395

396 1. *Delayed Release Products*

397

398 A *delayed release* drug product is a dosage form that releases a drug at a time later than
399 immediately after administration (e.g., the drug product exhibits a lag time in quantifiable
400 plasma concentrations). Typically, the coatings (e.g., enteric coatings) have been designed to
401 delay the release of medication until the dosage form has passed through the acidic medium of
402 the stomach. In vivo tests for delayed release drug products are similar to those for extended
403 release drug products. We recommend that in vitro dissolution tests for these products
404 document that they are stable under acidic conditions and that they release the drug only in a
405 neutral medium (e.g., pH 6.8).

406

407 2. *Extended Release Products*

408

409 An extended release drug product is a dosage form that allows a reduction in dosing frequency
410 and reduces fluctuations in plasma concentrations when compared to an immediate release
411 dosage form. Extended release products can be formulated as capsules, tablets, granules, pellets,

²¹ Ibid.

²² See footnote 3.

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412 or suspensions. If any part of a drug product includes an extended release component, the
413 product should be treated as a modified release dosage form for the purposes of establishing BE,
414 as specified below.

415

416 3. *Bioequivalence Studies*

417

418 For modified release products, we recommend the following studies: (1) a single-dose, fasting
419 study comparing the highest strength of the test with the RLD, and (2) a single-dose fed BE
420 study comparing the highest strength of the test with the RLD product. Because single-dose
421 studies are considered more sensitive in addressing the primary question of BE (e.g., release of
422 the drug substance from the drug product into the systemic circulation), multiple-dose studies are
423 generally not recommended.

424

425 4. *Demonstration of Bioequivalence: Additional Strengths*

426

427 Additional strengths of modified release products may be demonstrated to be bioequivalent to
428 the corresponding reference product strengths under 21 CFR 320.24(b)(6) if all of the following
429 conditions have been met:

430

- 431 • The additional strength is proportionally similar in its active and inactive
432 ingredients to the test product strength that underwent acceptable in vivo
433 studies.
- 434 • The additional strength has the same drug release mechanism as the strength
435 of the test product that underwent an acceptable in vivo study.
- 436 • Dissolution testing of all strengths is acceptable. We recommend that the
437 drug products exhibit similar dissolution profiles between the strength on
438 which BE testing was conducted and other strengths based on the f_2 test in at
439 least three dissolution media (e.g., pH 1.2, 4.5, and 6.8).²³

440

441 We recommend that applicants generate dissolution profiles on the test and RLD products of all
442 strengths.

443

444 5. *Postapproval Changes*

445

446 Please refer to FDA's guidance for industry *SUPAC: Modified Release Solid Oral Dosage*
447 *Forms, Chemistry Manufacturing and Controls; In Vitro Dissolution Testing and In vivo*
448 *Bioequivalence Documentation* for information regarding BE testing recommended for specified
449 types of postapproval changes for modified release dosage forms.²⁴

450

451 For postapproval changes, we recommend that applicants make an in vitro comparison between
452 the approved (prechange) product and the test (postchange) product. If appropriate, we

453

²³ In such instances, we anticipate that such approach will be adequate to demonstrate BE. See 21 CFR 320.24(b)(6).

²⁴ See footnote 3.

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455 recommend that you use an f_2 test to compare dissolution profiles. An in vivo BE study may be
456 needed if dissolution profiles are not shown to be similar. When in vivo BE studies are
457 recommended to support a postapproval change for an ANDA product, FDA recommends that
458 applicants compare the postchange ANDA drug product to the RLD and not to the prechange
459 ANDA product.

460

E. Chewable Tablets

461

462 Applicants should administer chewable tablets according to the directions on the label. If the
463 label states that the tablet must be chewed before swallowing, the product should be chewed
464 when administered in BE studies. If the label gives the option of either chewing the product or
465 swallowing it whole, the product should be swallowed whole, with 240 mL of water, when
466 administered in BE studies. We also recommend that you conduct in vitro dissolution testing on
467 intact, whole tablets of the chewable drug product.
468

469

470

V. SPECIAL TOPICS

471

472 There are a number of topics that may call for special consideration addressed in the following
473 sections. Additional questions should be referred to OGD.
474

475

A. Moieties to Be Measured

476

1. Parent Drug Versus Metabolites

477

478 The parent drug in the dosage form should always be measured in the biological fluids collected
479 in BE studies, unless accurate assay quantitation is not possible using state-of-the-art-technology.
480 We generally recommend that applicants measure only the parent drug, rather than metabolites,
481 because the concentration-time profile of the parent drug is more sensitive to changes in
482 formulation performance than a metabolite, which is more reflective of metabolite formation,
483 distribution, and elimination. Primary metabolite(s), formed directly from the parent compound,
484 should be measured if they are both: (1) formed substantially through presystemic metabolism
485 (first-pass, gut wall, or gut lumen metabolism) and (2) contribute significantly to the safety and
486 efficacy of the product. This approach should be used for all drug products, including pro-drugs.
487 We recommend that applicants analyze the parent drug measured in these BE studies using a
488 confidence interval (CI) approach. You can use the metabolite data to provide supportive
489 evidence of a comparable therapeutic outcome.
490

491

492 If the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or
493 serum for an adequate length of time, the metabolite data obtained from these studies should be
494 subject to the CI approach for BE demonstration.
495

496

2. Enantiomers Versus Racemates

497

498 For BE studies, we recommend using an achiral assay to measure the *racemate*. We only
499 recommend measuring individual enantiomers in BE studies when all of the following conditions
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501 have been met: (1) the enantiomers exhibit different pharmacodynamic characteristics, (2) the
502 enantiomers exhibit different pharmacokinetic characteristics, (3) primary efficacy and safety
503 activity reside with the minor enantiomer, and (4) nonlinear absorption is present (as expressed
504 by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at
505 least one of the enantiomers. In such cases where all of these conditions are met, we recommend
506 that applicants apply BE analysis to the enantiomers separately.

3. *Drug Products with Complex Mixtures as the Active Ingredients*

509
510 Certain drug products contain complex drug substances (e.g., active moieties or active
511 ingredients that are mixtures of multiple synthetic and/or natural source components). Some or
512 all of the components of these complex drug substances cannot be fully characterized with regard
513 to chemical structure and/or biological activity. We do not encourage quantification of all active
514 or potentially active components in pharmacokinetic studies. Rather, we recommend that
515 applicants base BE studies on a small number of markers of rate and extent of absorption.
516 Selection of the markers should be based on the characteristics of the drug product. Criteria for
517 marker selection can include amount of the moiety in the dosage form, plasma, or blood levels of
518 the moiety, and biological activity of the moiety relative to other moieties in the complex
519 mixture.

B. Long Half-Life Drugs

522
523 For an oral immediate release product with a long elimination half-life drug (>24 hrs), applicants
524 can conduct a single-dose, crossover study, provided an adequate washout period is used. If the
525 crossover study is problematic, applicants should use a BE study with a parallel design. For
526 either a crossover or parallel study, sample collection time should be adequate to ensure
527 completion of gastrointestinal transit of the drug product and absorption of the drug substance.
528 (which usually occurs within approximately 2 to 3 days). You can use C_{max} and a suitably
529 truncated AUC to characterize peak and total drug exposure, respectively. For drugs that
530 demonstrate low intrasubject variability in distribution and clearance, you can use an AUC
531 truncated at 72 hours ($AUC_{0-72\text{ hr}}$) in place of AUC_{0-t} or AUC_{0-inf} . For drugs demonstrating high
532 intrasubject variability in distribution and clearance, AUC truncation should not be used.

C. First Point C_{max}

535
536 The first point of a concentration-time curve in a BE study, based on blood and/or plasma
537 measurements, is sometimes the highest point, which raises questions of bias in the estimation of
538 C_{max} because of insufficient early sampling times. A carefully conducted pilot study can enable
539 an applicant to avoid this problem.

540
541 In the main BE study, collection of blood samples at an early time point, between 5 and 15
542 minutes after dosing, followed by additional sample collections (e.g., two to five) in the first
543 hour after dosing is usually sufficient to assess peak drug concentrations. Failure to include early
544 (5-15 minute) sampling times leading to first time-point C_{max} values may result in FDA not
545 considering the data for affected subjects from the analysis.

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547 **D. Alcoholic Beverage Effects On Modified Release Drug Products**

548
549 The consumption of alcoholic beverages can affect the release of a drug substance from an MR
550 formulation. The formulation can lose its modified release characteristics, leading to more rapid
551 drug release and altered systemic exposure. This can have deleterious effects on the drug's safety
552 and/or efficacy.

553
554 FDA recommends applicants developing certain extended release solid oral dosage forms to
555 conduct in vitro studies to determine the potential for dose dumping in alcohol in vivo. In vitro
556 assessments of the drug release from the drug product using media with various alcohol
557 concentrations may be recommended. An in vivo BE study of the drug product when
558 administered with alcohol may be suggested in some cases. For information on specific
559 products, we recommend that applicants consult the guidance for industry *Individual Product*
560 *Bioequivalence Recommendations* and any available relevant product-specific guidance.²⁵

561 **E. Endogenous Compounds**

562
563 Endogenous compounds are drugs that are already present in the body either because the body
564 produces them or they are present in the normal diet. Because these compounds are identical to
565 the drug that is being administered, determining the amount of drug released from the dosage
566 form and absorbed by each subject can be difficult. We recommend that applicants measure and
567 approximate the baseline endogenous levels in blood (plasma) and subtract these levels from the
568 total concentrations measured from each subject after the drug product has been administered. In
569 this way, you can achieve an estimate of the actual drug availability from the drug product.
570 Depending on whether the endogenous compound is naturally produced by the body or is present
571 in the diet, the recommended approaches for determining BE differ as follows:

- 572
573
- 574 • When the body produces the compound, we recommend that you measure multiple
575 baseline concentrations in the time period before administration of the study drug and
576 subtract the baseline in an appropriate manner consistent with the pharmacokinetic
577 properties of the drug.
 - 578
579 • When there is dietary intake of the compound, we recommend that you strictly
580 control the intake both before and during the study. Subjects should be housed at a
581 clinic before the study and served standardized meals containing an amount of the
582 compound similar to that in the meals to be served on the pharmacokinetic sampling
583 day.

584
585 For both of the approaches above, we recommend that you determine baseline concentrations for
586 each dosing period that are period specific. If a baseline correction results in a negative plasma
587 concentration value, the value should be set equal to 0 before calculating the baseline-corrected
588 AUC. Pharmacokinetic and statistical analysis should be performed on both uncorrected and
589 corrected data. Determination of BE should be based on the baseline-corrected data.

²⁵ See footnote 3.

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F. Orally Administered Drugs Intended For Local Action

In some cases, when a drug substance produces its effects by local action in the gastrointestinal tract, it may be appropriate to determine BE using PK endpoints. In other cases, it may be appropriate to determine BE using clinical endpoints, pharmacodynamic endpoints and/or suitably designed and validated in vitro studies in addition to, or instead of, measuring drug plasma concentrations. For information on specific products, we recommend that applicants consult the guidance for industry *Bioequivalence Recommendations for Specific Products* and any available relevant product-specific guidance.²⁶

G. In Vitro Dissolution Testing

The following guidances for industry provide recommendations on the development of dissolution methodology, setting specifications, and the regulatory applications of dissolution testing:²⁷

- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*
- *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*

1. Immediate Release Products

For immediate release drug products, we recommend that applicants submit the method set forth in any related official United States Pharmacopeia (USP) drug product monograph. If there is not an official monograph for your proposed product, we recommend that you use the FDA-recommended and the methods described in the USP general chapter on dissolution.²⁸ A dissolution methods database describing FDA-recommended and USP methods is available to the public on the following Web site at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>.

If you choose to develop a new dissolution method, we recommend that you include the following information in the submission:

- The pH solubility profile of the drug substance.
- Dissolution profiles generated at different agitation speeds (e.g., 100 to 150 revolutions per minute (rpm)) for USP Apparatus I (basket), or 50 to 100 rpm for USP Apparatus II (paddle).
- Dissolution profiles generated on all strengths in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8 buffer). Water can be used as an additional

²⁶ Ibid.

²⁷ See footnote 3.

²⁸ USP General Chapter <711> *Dissolution*.

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632 medium. If the drug being considered is poorly soluble, we recommend using
633 appropriate concentrations of surfactants.

634

635 2. *Modified Release Products*

636

637 For modified release products, dissolution profiles using the method set forth in the official USP
638 drug product monograph for the proposed product can be submitted. If there is not a USP drug
639 product monograph for your proposed product, we recommend that applicants use either the
640 FDA-recommended method (see the dissolution methods database mentioned above), or develop
641 a method that is specific for your product. In addition, we recommend that you submit profiles
642 using the methods described in the USP general chapter on dissolution or FDA methods in
643 addition to those three described above (e.g., pH 1.2, 4.5 buffer, and 6.8 buffer). If you are
644 proposing a method different from the FDA-recommended or USP method, we recommend that
645 you submit data using the FDA-recommended or USP method in addition to your proposed
646 method for comparison.

647

648 The applicant should select the agitation speed and medium that provide adequate discriminating
649 ability, taking into account all the available in vitro and in vivo data.

650

651 We recommend that you use dissolution data from three newly manufactured batches of test
652 product to set dissolution specifications for modified release dosage forms.

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ATTACHMENT: GENERAL DESIGN AND DATA HANDLING OF BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS

For both replicate and nonreplicate in vivo pharmacokinetic BE studies, we recommend the following general approaches. Elements can be adjusted for certain drug substances and drug products.

Study conduct:

- The test or RLD products can be administered with about 8 ounces (240 mL) of water to an appropriate number of subjects under fasting conditions, unless the study is a fed BE study.
- Fed Treatments: We recommend that subjects start the recommended meal 30 minutes before administration of the drug product following an overnight fast of at least 10 hours. Study subjects should eat this meal in 30 minutes or less and the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 8 fluid ounces (240 mL) of water.
- No food should be allowed for at least 4 hours postdose. Water will be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.
- Generally, the highest-marketed strength can be administered as a single unit. If warranted to achieve sufficient bioanalytical sensitivity, multiple units of the highest strength can be administered, provided the total single dose remains within the labeled dose range and the total dose is safe for administration to the study subjects.
- An adequate washout period (e.g., more than five half-lives of the moieties to be measured) should separate each treatment.
- The lot numbers of both test and RLD products and the expiration date for the RLD product should be stated. We recommend that the assayed drug content of the test product batch not differ from the RLD product by more than +/- 5 percent. The applicant should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and RLD products. In accordance with 21 CFR 320.63, study drug test article of the test and RLD products must be retained for five years. For additional information, please refer to the guidance for industry *Handling and Retention of Bioavailability and Bioequivalence Testing Samples*.²⁹
- Before and during each study phase, we recommend that subjects: (1) be allowed water as desired, except for 1 hour before and after drug administration, (2) be provided

²⁹ See footnote 3.

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697 standardized meals no less than 4 hours after drug administration, and (3) abstain from
698 alcohol for 24 hours before each study period and until after the last sample from each
699 period has been collected.

700

Fed studies test meal composition:

702

703 We recommend that applicants conduct fed BE studies using meals that provide the greatest
704 effects on gastrointestinal (GI) physiology and systemic drug availability. We recommend a
705 high-fat (approximately 50 percent of total caloric content of the meal), high-calorie
706 (approximately 800 to 1000 calories) test meal for fed BE studies. This test meal should derive
707 approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.³⁰
708 The caloric breakdown of the test meal should be provided in the study report.

709

Sample collection and sampling times:

711

712 We recommend that under normal circumstances, applicants sample blood, rather than urine or
713 tissue. In most cases, drug or metabolites are measured in serum or plasma. However, in certain
714 cases, whole blood may be more appropriate for analysis. We recommend drawing blood
715 samples at appropriate times to describe the absorption, distribution, and elimination phases of
716 the drug. For most drugs, we recommend collecting 12 to 18 samples, including a predose
717 sample, per subject, per dose. This sampling should continue for at least three or more terminal
718 elimination half-lives of the drug. The exact timing for sample collection depends on the nature
719 of the drug and the rate of input from the administered dosage form. The sample collection can
720 be spaced in such a way that the maximum concentration of drug in the blood (C_{max}) and
721 terminal elimination rate constant (K_{el}) can be estimated accurately. At least three to four
722 samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of
723 λ_z from linear regression. We recommend recording the actual clock time when samples are
724 drawn as well as the elapsed time related to drug administration.

725

Subjects with predose plasma drug concentrations:

727

728 If the predose concentration is ≤ 5 percent of C_{max} value in a subject with predose plasma
729 concentration, you can include the subject's data without any adjustments in all pharmacokinetic
730 measurements and calculations. We recommend that if the predose value is greater than 5
731 percent of C_{max} , you drop the subject from all BE study evaluations.

732

Data deletion because of vomiting:

734

735 We recommend that data from subjects who experience emesis during the course of a BE study
736 for immediate release products be deleted from statistical analysis if vomiting occurs at or before
737 2 times median T_{max} . For modified release products, we recommend deleting data from the
738 analysis if a subject vomits during a period of time less than or equal to the dosing interval stated

³⁰ An example test meal would be: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal (e.g., beef or chicken instead of bacon) can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume, density, and viscosity.

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739 in the labeling of the product.

740

741 **We recommend applicants provide the following pharmacokinetic information in their**
742 **submissions:**

743

744 • Plasma concentrations and time points

745 • Subject, period, sequence, treatment

746 • Intersubject, intrasubject, and/or total variability, if available

747 • For single-dose BE studies: AUC_{0-t} , AUC_{0-inf} , and C_{max} . In addition, please report the
748 following supportive information: T_{max} , K_{el} and $t_{1/2}$.

749 • For steady-state BE studies: AUC_{0-tau} and C_{maxSS} . In addition, please report C_{minSS}
750 (concentration at the end of a dosing interval), C_{avSS} (average concentration during a
751 dosing interval), degree of fluctuation $[(C_{max}-C_{min})/C_{avSS}]$, swing $[(C_{maxSS}-C_{minSS})/C_{minSS}]$,
752 and T_{max} .

753

754 **We recommend applicants provide the following statistical information for AUC_{0-t} ,**
755 **AUC_{0-inf} , and C_{max} :**

756

757 • Geometric means

758 • Arithmetic means

759 • Geometric mean ratios

760 • 90 percent Confidence intervals (CI)

761

762 We also recommend that you provide logarithmic transformation for measures used for BE
763 demonstration.

764

765 **Rounding off of CI values:**

766

767 We recommend that applicants not round off CI values; therefore, to pass a CI limit of 80 to 125
768 percent, the value would be at least 80.00 percent and not more than 125.00 percent.

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GLOSSARY

AUC_{0-t} - Area under the concentration time curve from time zero to the last measurable time point.

AUC_{0-inf} - Area under the concentration time curve extrapolated to infinity.

AUC_{0-tau} - Area under the concentration time curve for one dosing interval at steady-state.

C_{avSS} - Average plasma concentration at steady-state.

C_{max} - Peak concentration.

C_{maxSS} - Peak concentrations during the dosing interval at steady-state.

C_{minSS} - Minimum or trough concentrations at steady-state.

Enantiomers - Two stereoisomers (molecules that are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms) that are related to each other by a reflection: they are mirror images of each other, which are nonsuperimposable. Every stereocenter in one has the opposite configuration in the other. Two compounds that are enantiomers of each other have the same physical properties, except for the direction in which they rotate the polarized light and how they interact with different optical isomers of other compounds.

Racemate - A racemate is optically inactive. Because the two isomers rotate plane-polarized light in opposite directions, they cancel out; therefore, a racemic mixture does not rotate plane-polarized light. In contrast to the two separate enantiomers, which generally have identical physical properties, a racemate often has different properties compared to either one of the pure enantiomers. Different melting points and solubilities are very common, but differing boiling points are also possible. Pharmaceuticals can be available as a racemate or as a pure enantiomer, which might have different potencies.