
Guidance for Industry

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product

DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)**

**May 2014
Biosimilars**

Guidance for Industry

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1 **Guidance for Industry¹**
2 **Clinical Pharmacology Data to Support a Demonstration of**
3 **Biosimilarity to a Reference Product**
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6 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
11 the appropriate number listed on the title page of this guidance.
12

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15 **I. INTRODUCTION**
16

17 This draft guidance is intended to assist sponsors with the design and use of clinical
18 pharmacology studies to support a decision that a proposed therapeutic biological product is
19 *biosimilar* to its reference product. This guidance pertains to those products—such as
20 therapeutic biological products—for which pharmacokinetic (PK) and pharmacodynamic (PD)
21 data are required as part of a stepwise approach to developing the data and information necessary
22 to support a demonstration of biosimilarity. Specifically, the guidance discusses some of the
23 overarching concepts related to clinical pharmacology testing for biosimilar products,
24 approaches for developing the appropriate clinical pharmacology database, and the utility of
25 modeling and simulation for designing clinical trials.
26

27 In its final form, this guidance will be one in a series that FDA is developing to implement the
28 Biologics Price Competition and Innovation Act of 2009 (BPCI Act).² It is intended to assist
29 sponsors in designing clinical pharmacology studies that can support an application submitted
30 under section 351(k) of the Public Health Service Act (PHS Act). Some scientific principles
31 described in this guidance may also be informative for the development of certain biological
32 products under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),³ but

¹ This draft guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at FDA.

² Sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Affordable Care Act), Public Law 111-148.

³ A 505(b)(2) application is a new drug application (NDA) that contains full reports of investigations of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use (e.g., the Agency’s finding of safety and/or effectiveness for a listed drug or a published study not conducted by or for the applicant). A 505(b)(2) application that seeks to rely on a listed drug (i.e., the reference product) must contain adequate data and information to demonstrate that the proposed product is sufficiently similar to the listed drug to justify reliance, in part, on FDA’s finding of safety and/or effectiveness for the listed drug. Any aspects of the proposed product that differ from the listed drug must be supported by adequate data and information to show that the differences do not affect the safety and effectiveness of the proposed product.

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33 no particular relationship between the standards for approval under these separate statutory
34 schemes is implied.

35
36 FDA’s guidance documents, including this guidance, do not establish legally enforceable
37 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
38 be viewed only as recommendations, unless specific regulatory or statutory requirements are
39 cited. The use of the word *should* in Agency guidances means that something is suggested or
40 recommended, but not required.

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II. THE ROLE OF CLINICAL PHARMACOLOGY STUDIES IN THE 44 DEMONSTRATION OF BIOSIMILARITY

45

46 The BPCI Act, which was enacted as part of the Patient Protection and Affordable Care Act
47 (Affordable Care Act), established an abbreviated pathway for FDA licensure of biological
48 products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed
49 reference product. The term *biosimilarity* is defined in section 351(i) of the PHS Act to mean
50 that the biological product is “highly similar to the reference product notwithstanding minor
51 differences in clinically inactive components and that there are “no clinically meaningful
52 differences between the biological product and the reference product in terms of the safety,
53 purity, and potency of the product.”⁴

54

55 Under section 351(k)(2) of the PHS Act, a 351(k) application must contain, among other things,
56 information demonstrating that the biological product is biosimilar to a reference product (a
57 biological product already licensed under section 351(a) of the PHS Act) based on data derived
58 from analytical studies; animal studies; and a clinical study or clinical studies, including the
59 assessment of immunogenicity and PK and PD;⁵ unless FDA determines, in its discretion, that
60 certain studies are unnecessary in a 351(k) application.⁶

61

62 Clinical pharmacology studies are normally a critical part of demonstrating biosimilarity by
63 supporting a demonstration that there are no clinically meaningful differences between the
64 proposed biosimilar and the reference product. These studies provide the data that describe the
65 degree of similarity in drug exposure between the proposed biosimilar and the reference product.
66 In addition, clinical pharmacology studies often include PD endpoints (both therapeutic and
67 toxic) and pharmacometric analysis to assess whether or not there are clinically meaningful
68 differences between the proposed biosimilar and the reference product. If done well, they can
69 add to the totality of the evidence, reduce residual uncertainty, and thus guide the need for and
70 design of subsequent clinical testing to successfully support a demonstration of no clinically
71 meaningful differences in the overall demonstration of biosimilarity. Clinical pharmacology data
72 may be an important component of the scientific justification supporting extrapolation of clinical
73 data to one or more additional conditions of use.⁷

⁴ Section 351(i)(2) of the PHS Act.

⁵ Section 351(k)(2)(A)(i)(I) of the PHS Act.

⁶ Section 351(k)(2)(A)(iii) of the PHS Act.

⁷ See FDA’s draft guidance for industry *Q & As Regarding Implementation of the BPCI Act of 2009* for more information on this topic. When finalized, the guidance will reflect FDA’s current thinking on this issue. The

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74
75 The types of clinical pharmacology studies to be conducted will depend on the residual
76 uncertainties about biosimilarity that these studies are capable of addressing in the context of the
77 overall program for biosimilar product development.

78
79 For a list of definitions of terms specific to development of biosimilar products, see the
80 Definitions section at the end of this draft guidance.

81
82

83 **III. CRITICAL CONSIDERATIONS IN THE USE OF CLINICAL** 84 **PHARMACOLOGY STUDIES TO SUPPORT BIOSIMILARITY**

85
86 Three key concepts, exposure and response assessment, evaluation of residual uncertainty, and
87 assumptions about analytical quality and similarity, are especially relevant to development of
88 proposed biosimilar products and are discussed in more detail in this section. Bioanalytical
89 methodology and the use of clinical pharmacology studies to gain safety and immunogenicity
90 information are also examined.

91 92 **A. Exposure and Response Assessment to Support a Demonstration of Biosimilarity**

93
94 The objective of a well-designed clinical PK and PD study in a biosimilar development program
95 is to evaluate the similarities and differences in the PK and PD profiles between the proposed
96 biosimilar product and the reference product. Exposure-response information is important for
97 the determination of safety, purity, and potency of any biological product, as well as for the
98 determination of any potential clinically meaningful difference between two products.
99 Determining the response to exposure to a biological product is particularly challenging, because
100 the active product is not a single chemical and/or its active metabolites; rather, it is a mixture of
101 closely related, complex biological substances that, in aggregate, make up the active component.

102
103 For the purposes of this guidance, we use the broad term *exposure* to refer to PK variables,
104 including input of all active components of the biological product as measured by dose (drug
105 input to the body) and various measures of single or integrated drug concentrations in plasma
106 and other biological fluid, e.g., peak concentration (C_{max}), lowest concentration measured
107 following dosing (C_{min}), concentration prior to the next dose during multiple dosing ($C_{trough\ ss}$),
108 and area under the plasma/blood concentration-time curve (AUC). *Response*, referred to here as
109 PD, is a direct measure of the pharmacological or toxicological effect of a drug. Clinical
110 pharmacology similarity may include assessments of PK similarity, and PD similarity.

111
112 The PD marker(s) used to measure response may be a single biomarker or a composite of
113 markers that effectively demonstrate the characteristics of the product's target effects. Use of a
114 single, scientifically acceptable, established PD marker or a composite of more than one relevant
115 PD marker, can reduce residual uncertainty with respect to clinically meaningful differences

guidances referenced in this document are available on the FDA Drugs guidance Web page 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 the FDA Drugs guidance Web page.

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116 between products and add significantly to the overall demonstration of biosimilarity. Using
117 broader panels of biomarkers (e.g., by conducting a protein or mRNA microarray analysis) that
118 capture multiple pharmacological effects of the product may be of additional value. When
119 determining which markers should be used to measure response, it is important to consider the
120 following:

- 121
- 122 • The time of onset of the PD marker relative to dosing
- 123 • The dynamic range of the PD marker over the exposure range to the biological
124 product
- 125 • The sensitivity of the PD marker to differences between the proposed biosimilar
126 product and the reference product
- 127 • The relevance of the PD marker to the mechanism of action of the drug
- 128 • The relationship between changes in the PD marker and clinical outcomes
- 129

130 If these criteria are addressed, through the submission of convincing PK and PD results, the
131 extent of the clinical development program can be refined in both the design and extent of
132 additional clinical trials necessary to assess whether there are clinically meaningful differences
133 between the proposed biosimilar product and the reference product. It is important to note that in
134 some instances PD markers with the relevant characteristics listed above have not been
135 identified, but the sponsor is encouraged to incorporate PD biomarkers that correlate well with
136 drug exposure over a wide concentration range as these represent potentially orthogonal tests that
137 may be supportive of clinical pharmacology similarity. When PD markers are not sensitive or
138 specific enough to be used to assess for clinically meaningful differences, the derived PK
139 parameters should be used as the primary basis for evaluating similarity from a clinical
140 pharmacology perspective, and the PD markers may be used to augment the PK data. A
141 combination of PK and PD similarity representing orthogonal biosimilarity, may be an important
142 assessment in demonstrating no clinically meaningful differences.

B. Evaluation of Residual Uncertainty

143

144

145

146 In evaluating a sponsor's data to support a demonstration of biosimilarity, using a risk-based
147 approach, FDA will consider the totality of the data and information submitted, including, for
148 example, data from the structural and functional characterization, nonclinical evaluations, human
149 PK and PD studies, clinical immunogenicity testing, and investigation of clinical safety and
150 when necessary clinical effectiveness. These data should be collected in a stepwise manner.
151 Especially pertinent to FDA's clinical pharmacology evaluation is the clinical PK and PD data
152 and safety data obtained in conjunction with the clinical pharmacology studies. The need for
153 additional studies at each step in this progressive approach will be determined by the degree of
154 residual uncertainty that remains at each step regarding the similarity of the products and
155 whether or not the study can address these uncertainties.

C. Assumptions About Analytical Quality and Similarity

156

157

158

159 In a stepwise assessment of biosimilarity, extensive and robust comparative structural and
160 functional studies (e.g. bioassays, binding assays, and studies of enzyme kinetics) should be
161 performed to evaluate whether the proposed biosimilar product and the reference product are

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162 highly similar. A meaningful assessment depends on, among other things, the capabilities of
163 available state-of-the-art analytical assays to assess, for example, the molecular weight of the
164 protein, its higher order structure and post-translational modifications, heterogeneity, functional
165 properties, impurity profiles, and degradation profiles denoting stability. The sponsor should
166 describe the capabilities and limitations of the methods used in the analytical assessment.
167

168 An extensive analytical characterization may reveal differences between the proposed biosimilar
169 product and the reference product. The type, nature, and extent of any differences between the
170 two products should be clearly identified, and the potential effect of these differences should be
171 addressed and supported by appropriate data. In some cases, additional studies may demonstrate
172 that the identified difference is within an acceptable range to consider the proposed biosimilar
173 product to be highly similar to the reference product. However, certain differences in the results
174 of the analytical characterization may preclude a determination by FDA that the proposed
175 biosimilar product is highly similar to the reference product and, therefore, its further
176 development through the 351(k) regulatory pathway is not recommended.
177

178 It may be useful to compare the quality attributes of the proposed biosimilar product with those
179 of the reference product using a meaningful fingerprint-like analysis algorithm that covers a
180 large number of product attributes and their combinations with high sensitivity using orthogonal
181 methods. Such a strategy can further quantify the overall similarity between two products and
182 may provide a basis for a more selective and targeted approach to subsequent animal and/or
183 clinical studies.
184

185 The result of the comparative analytical characterization may lead to one of four assessments
186 within a development-phase continuum:
187

- 188 • Not similar: Certain differences in the results of the analytical characterization may
189 lead to an assessment of “not similar” and further development through the 351(k)
190 regulatory pathway is not recommended unless, for example, modifications are made
191 to the manufacturing process for the proposed biosimilar product that is likely to lead
192 to a highly similar biological product.
193
- 194 • Similar: Further information is needed to determine if the product is highly similar to
195 the reference product. Additional analytical data or other studies are necessary to
196 determine if observed differences are within an acceptable range to consider the
197 proposed biosimilar product to be highly similar to the reference product. As an
198 example, glycosylation plays an important role in the PK of certain protein products.
199 Manufacturing process conditions may impact glycosylation. Comparative PK and
200 PD studies of the proposed biosimilar product and the reference product help resolve
201 that some differences in glycosylation identified in the analytical studies would be
202 within an acceptable range to consider the proposed biosimilar product to be highly
203 similar to the reference product.
204
- 205 • Highly similar: The proposed biosimilar product meets the statutory standard for
206 analytical similarity. The results of the comparative analytical characterization
207 permit high confidence in the analytical similarity of the proposed biosimilar and the

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208 reference product, and it would be appropriate for the sponsor to conduct targeted and
209 selective animal and/or clinical studies to resolve residual uncertainty and support a
210 demonstration of biosimilarity.

211

- 212 • Highly similar with fingerprint-like similarity: The proposed biosimilar product meets
213 the statutory standard for analytical similarity based on integrated, multi-parameter
214 approaches that are extremely sensitive in identifying analytical differences. The
215 results of these fingerprint-like analyses permit a very high level of confidence in the
216 analytical similarity of the proposed biosimilar and the reference product, and it
217 would be appropriate for the sponsor to use a more targeted and selective approach to
218 conducting animal and/or clinical studies to resolve residual uncertainty and support a
219 demonstration of biosimilarity.

220

221 The outcome of the comparative analytical characterization should inform the next steps in the
222 demonstration of biosimilarity.

D. Integrity of the Bioanalytical Methods Used in PK and PD Studies

225

226 When performing an evaluation of clinical pharmacology similarity, it is critical to use the
227 appropriate bioanalytical methods to evaluate the PK and PD properties of a proposed biosimilar
228 product and its reference product. Because of the complex molecular structure of biological
229 products, conventional analytical methods used for chemical drugs may not be suitable for
230 biological products. The bioanalytical methods used for PK and PD evaluations should be
231 accurate, precise, specific, sensitive, and reproducible. The scientific requirements of
232 bioanalytical methods have been described in a separate guidance document.⁸

1. General PK Assay Considerations

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234

235

236 A sponsor should design or choose an assay based on a thorough understanding of the
237 mechanism of action and/or structural elements of the proposed biosimilar product and reference
238 product critical for activity. Analytical assays should be able to detect the active and/or free
239 product instead of the total product, particularly if binding to a soluble ligand is a necessary step
240 for activity and clinical effect. The inability to develop such an assay should be supported with
241 justification as to why failure to detect free and/or active forms does not compromise the PK
242 similarity assessment.

2. General PK and PD Assay Considerations

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247 Sponsors should make every effort to employ the most suitable assays and methodologies with
248 the aim of obtaining data that are meaningful and reflective of drug exposure, the biological
249 activity, and/or the PD effect of the proposed biosimilar product and the reference product.
250 Furthermore, the sponsor should provide a rationale for the choice of assay and the relevance of
251 the assay to drug activity in submissions to the FDA.

⁸ FDA guidance for industry *Bioanalytical Method Validation*.

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3. *Specific Assays*

Three types of assays are of particular importance for biosimilar product development: ligand binding assays, concentration and activity assays, and PD assays.

- Ligand binding assays

Currently, the concentration of most biological products in circulation is measured using ligand binding assays. These assays are analytical methods in which quantification is based on macromolecular interactions with assay reagents, such as antibodies, receptors or ligands that bind with adequate affinity and selectivity to the biological product. The ligand binding assay reagents chosen for capturing and detecting the biological product should be carefully evaluated with the goal of producing product concentration data that are meaningful to, and reflective of, the pharmacological activity and/or PD effect of the biological product of interest. Some biological products exert pharmacological effects only after multiple molecular interactions. In some cases, monoclonal antibodies, bispecific antibodies, or fusion proteins bind to ligand or receptor proteins through the target antigen binding epitope of the molecule and to FcγR with the crystallizable fragment (Fc) portion of the molecule. A sponsor should choose the most appropriate interactions to measure.

Generally, assays for monoclonal antibody product concentrations rely on molecular interactions involving the antigen binding (Fab) region, in particular epitopes in the complementarity determining regions (CDRs). Antibody-based assays for biological products that rely on epitopes involved in pharmacological/biochemical interactions with targets are most likely to produce concentration data that are meaningful with respect to target binding activity.

- Concentration and activity assays

Bioanalytical methods that are not based on ligand binding can be used for quantification of the proposed biosimilar product and reference product concentrations. For some biological products, such as those that are used to achieve enzyme replacement, the drug availability measurements may rely on activity and should be captured through an appropriate activity assay. Depending on the complexity of the structural features, some biological products may need more than one assay to fully characterize the systemic exposure of the proposed biosimilar product and reference product. In such cases, mass spectrometry and other assays may be useful in distinguishing the structures of product variants.

- PD assays

Relevant PD markers may not always be available to support a proposed biosimilar product's development through clinical pharmacology studies. However, when PD assessment is a component of the biosimilarity evaluation, sponsors should provide a

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298 rationale for the selection of the PD endpoints and/or markers, as well as data to
299 demonstrate the quality of the assay, in written communications to FDA. PD assays
300 should be sensitive for a product or product class and designed to quantitatively
301 evaluate the pharmacologic activity of the biologic product. Ideally, the activity
302 measured by the PD assay should be relevant to a clinical outcome; however the PD
303 assay should at least be relevant to a pharmacological effect of the biologic product.
304 If the selected PD endpoint(s) are not closely related to clinical outcome, use of
305 multiple complimentary PD assays may be most useful. Because the PD assay is
306 highly dependent on the pharmacological activity of the product, the approach for
307 assay validation and the characteristics of the assay performance may differ
308 depending on the specific PD assay. However, the general guiding principles for
309 choosing PK assays (i.e., demonstration of specificity, reliability, and robustness) also
310 apply to PD assays. Sponsors should provide supporting data for the choice of assay
311 and the justification of PD markers in submissions to FDA.

312

E. Safety and Immunogenicity

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314
315 In the context of this guidance, immunogenicity refers to an immune response to the biological
316 product that may result in immune-mediated toxicity and/or lack of effectiveness. Safety and
317 immunogenicity data from the clinical pharmacology studies should be collected and evaluated.
318 FDA recognizes that safety and immunogenicity data derived from these studies may need to be
319 supplemented by additional evaluations either preapproval or postapproval. However, as part
320 of their role in the overall assessment of biosimilarity, clinical pharmacology studies may
321 sometimes suggest that there are clinically meaningful differences between the products that may
322 inform the design and details of additional investigations and/or clinical studies conducted to
323 further investigate these potential differences. It is important to note that depending on the
324 extent of such potential differences, it may not be appropriate for additional studies to be
325 conducted in the context of a biosimilar development program.

326

327 Publicly available information on the safety and immunogenicity profile of a reference product
328 should be considered when incorporating safety and immunogenicity measurements in the
329 clinical pharmacology studies.⁹ For example, when a reference product is known to have the
330 potential for immune-mediated toxicity, assays capable of detecting binding antibodies (and their
331 neutralizing potential) should be developed in advance to analyze samples obtained from PK and
332 PD studies, so that immunogenicity may be evaluated in real time. Generally, samples can be
333 stored for future analysis if such assays are not yet developed.¹⁰ In either approach, sponsors
334 should carefully consider assay confounders, such as the systemic presence of the proposed
335 biosimilar or reference product. Recommendations for immunogenicity assay development have
336 been described in a separate guidance document.⁸

337

⁹ See FDA's draft guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* for more information on this topic. When finalized, the guidance will reflect FDA's current thinking on this issue.

¹⁰ FDA has issued the draft guidance for industry *Assay Development for Immunogenicity Testing of Therapeutic Proteins*. Once finalized, it will represent FDA's perspective on this topic.

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338 When evaluating data (e.g., safety, immunogenicity) collected during the PK and PD studies,
339 sponsors should have an understanding of the time course for the appearance and resolution of
340 safety signals or immune responses. The PK profile of the proposed biosimilar product and/or
341 the publicly available PK data for the reference product can be used to inform the duration of
342 follow-up for safety signals or immunogenicity.
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IV. DEVELOPING CLINICAL PHARMACOLOGY DATA FOR SUPPORTING A DEMONSTRATION OF BIOSIMILARITY

347

348 Sponsors are encouraged to discuss the crucial aspects of their clinical pharmacology
349 development plan with FDA in the early stages of the biosimilar development program. Some
350 critical study design issues that should be discussed with FDA are set forth below.
351

351

A. Study Design

352

353
354 To evaluate clinical PK and PD similarity for the development of proposed biosimilar products,
355 two study designs are of particular relevance: crossover designs and parallel study designs.
356

356

- 357 • Crossover design

358

359 For PK similarity assessments, a single-dose, randomized, crossover study is
360 generally the preferred design. A crossover study is recommended for a product with
361 a short half-life (e.g., shorter than 5 days), a rapid PD response (e.g., onset, maximal
362 effect, and disappearance in conjunction with drug exposure), and a low incidence of
363 immunogenicity. This design is considered the most sensitive to assess PK similarity,
364 and it can provide reliable estimates of differences in exposure with a minimum
365 number of subjects. For PD similarity assessments, multiple doses may be
366 appropriate when the PD effect is delayed or otherwise not parallel to the single-dose
367 drug PK profile. The time course of appearance and disappearance of
368 immunogenicity and its relation to the washout period is an issue for consideration for
369 studies using a crossover design.
370

370

- 371 • Parallel design

372

373 Many biological products have a long half-life and elicit immunogenic responses. A
374 parallel group design is appropriate for products that have a long half-life or for
375 which repeated exposures can lead to an increased immune response that can affect
376 the PK and/or PD similarity assessments. This design is also appropriate for diseases
377 that exhibit time-related changes associated with exposure to the drug.
378

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B. Reference Product

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381 The BPCI Act defines the *reference product* for a proposed biosimilar product as the single
382 biological product licensed under section 351(a) of the PHS Act against which a proposed
383 biosimilar product is evaluated in a 351(k) application.¹¹ As a scientific matter, analytical
384 studies and at least one clinical PK and, if appropriate, PD study, intended to support a
385 demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar
386 product directly with the U.S.-licensed reference product. However, a sponsor may use a non-
387 U.S. licensed comparator product in certain studies to support a demonstration that the proposed
388 biological product is biosimilar to the U.S.-licensed reference product. If a sponsor seeks to use
389 data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed
390 product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the
391 sponsor should provide adequate data or information to scientifically justify the relevance of
392 these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to
393 the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will
394 always include data from analytical studies (e.g., structural and functional data) that directly
395 compares all three products (i.e., (the proposed biosimilar product, the U.S.-licensed reference
396 product, and the non-U.S.-licensed product) and is likely to also include PK and, if appropriate,
397 PD study data for all three products .

398

C. Study Population

399

400
401 Healthy Volunteer vs. Patient: The study population selected should be the most informative for
402 detecting and evaluating differences in PK and PD profiles between the proposed biosimilar
403 product and the reference product. Human PK and PD studies should be conducted in healthy
404 volunteers if the product can be safely administered to this population. A study in healthy
405 volunteers is considered to be more sensitive in evaluating the product similarity because it is
406 likely to produce less PK variability compared with that in patients with potentially confounding
407 factors such as underlying and/or concomitant disease and concomitant medications. If safety or
408 ethical considerations preclude the participation of healthy volunteers in human PK and PD
409 studies for certain products (e.g., immunogenicity or known toxicity from the reference product),
410 or if PD markers would only be relevant in patients with the condition or disease, the clinical
411 pharmacology studies should be conducted in patients. In cases where PK and/or PD will be the
412 full assessment for clinically meaningful differences, a population that is representative of the
413 patient population to which the drug is targeted will be appropriate for the study.

414

415 Demographic Group: Clinical pharmacology studies should be conducted in the subject or
416 patient demographic group most likely to provide a sensitive measure of differences between the
417 proposed biosimilar product and the reference product. The sponsor should provide justification
418 for why the subject or patient group chosen for clinical pharmacology studies will provide the
419 most sensitive measure of difference between the proposed biosimilar and reference products.
420 The total number of subjects should provide adequate power for similarity assessment. Analysis
421 of the data from all subjects as one group represents the primary study endpoint, and a statistical
422 analysis of the data from the subgroups would be exploratory only.

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D. Dose Selection

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¹¹ See sections 351(i)(4) of the PHS Act.

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426 As in the selection of study population, the dose selected should be the most sensitive to detect
427 and evaluate differences in the PK and PD profiles between the proposed biosimilar product and
428 the reference product. The dose selected should be one most likely to provide clinically
429 meaningful and interpretable data. If a study is conducted in a patient population, the approved
430 dose for the reference product may be the appropriate choice, because this may best demonstrate
431 the pharmacological effects in a clinical setting. However, a lower dose in the steep part of the
432 exposure-response curve may be appropriate when PD is being measured or when healthy
433 subjects are selected for evaluation (See section V; Utility of Simulation Tools in Study Design
434 and Data Analysis).

435
436 In certain cases, a dose selected from a range of doses may be useful for a clinical PK and PD
437 similarity assessment. For example, if the concentration effect relationship of the reference
438 product is known to be highly variable or nonlinear, a range of doses can be used to assess dose-
439 response (see Section V; Utility of Simulation Tools in Study Design and Data Analysis).

440
441 If the product can only be administered to patients, an alternative dosing regimen such as a single
442 dose for a chronic indication or a lower dose than the approved dose, may be acceptable if the
443 approved dose results in nonlinear PK or exceeds the dose required for maximal PD effect, and
444 therefore will not allow for the detection of differences. However, the appropriateness of an
445 alternative dosing regimen will depend on certain factors, e.g., the lower dose is known to have
446 the same effect as the approved dose or if it is ethically acceptable to give lower doses
447 notwithstanding differences in effect. Adequate justification for the selection of an alternative
448 dosing regimen should be provided in written communication to FDA.

449
450 When appropriate, PD markers should be used to assess PK/PD similarity between a proposed
451 biosimilar product and the reference product. Development of a dose-response profile that
452 includes the steep part of the dose-response curve is a sensitive test for similarity between
453 products, and if clinical pharmacology similarity between products is demonstrated, in some
454 instances this may complete the clinical evaluation, and in others it may support a more targeted
455 clinical development program.

E. Route of Administration

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459 Human PK and PD studies should be conducted using the same route of administration for the
460 proposed biological product and the reference product. If more than one route of administration
461 (e.g., both intravenous and subcutaneous) is approved for the reference product, the route
462 selected for the assessment of PK and PD similarity should be the one most sensitive for
463 detecting clinically meaningful differences. In most cases, this is likely to be the subcutaneous
464 or other extravascular routes of administration, because extravascular routes can provide insight
465 into potential PK differences during the absorption phase in addition to the distribution and
466 elimination phases.

F. Pharmacokinetic Measures

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470 All PK measures should be obtained for the proposed biosimilar product and the reference
471 product. The sponsor should obtain measures of C_{max} and total exposure (AUC) in a relevant

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472 biological fluid. For single-dose studies, total exposure should be calculated as the area under
473 the biological product concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$), where
474 $AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el}$ (C_t --concentration at the last measurable timepoint divided by
475 k_{el} --elimination rate constant) is calculated based on an appropriate method. C_{max} should be
476 determined from the data without interpolation. For intravenous studies $AUC_{0-\infty}$ will be
477 considered the primary endpoint. For subcutaneous studies C_{max} and AUC will be considered
478 coprimary study endpoints. For multiple dose studies the measurement of total exposure should
479 be the area under the concentration-time profile from time zero to time tau over a dosing interval
480 at steady-state ($AUC_{0-\tau}$), where tau is the length of the dosing interval and this is considered the
481 primary endpoint. The steady state trough concentration ($C_{trough\ ss}$) should be measured at the end
482 of a dosing interval before initiating the next dose and C_{max} the maximum measured
483 concentration following the dose and these are considered secondary endpoints. Population PK
484 data will not provide an adequate assessment for PK similarity.

485

G. Pharmacodynamic Measures

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487 In certain circumstances, human PK and PD data that demonstrate similar exposure and response
488 between a proposed biosimilar product and the reference product may be sufficient to completely
489 assess clinically meaningful differences between products. This would be based on similar
490 pharmacodynamics using a PD measure that reflects the mechanism of drug action in cases
491 where the PD measure has a wide dynamic range over the range of drug concentrations achieved
492 during the PK study. In such instances, a full evaluation of safety and immunogenicity would
493 still be necessary, either before or after approval. When human PD data in a PK/PD study are
494 insufficient to completely assess for clinically meaningful differences, obtaining such data may
495 support a more targeted approach for the collection of subsequent clinical safety and
496 effectiveness data. Selection of appropriate time points and durations for the measure of PD
497 markers will depend on the characteristics of the PD markers (e.g., timing of PD response with
498 respect to product administration based on the half life of the product and anticipated duration of
499 effect). When a PD response lags after initiation of product administration, it may be important
500 to study multiple-dose and steady state conditions, especially if the proposed therapy is intended
501 for long-term use. Comparison of the PD marker(s) between proposed biosimilar product and
502 the reference product should be by determination of the area under the effect curve (AUEC). If
503 only one PD measurement is available due to the characteristics of the PD marker, it should be
504 linked to a simultaneous drug concentration measurement and this should be used as a basis for
505 comparison between products.

506

507 Use of a single, scientifically acceptable, established PD marker as described above, or a
508 composite of more than one relevant PD markers, can reduce residual uncertainty with respect to
509 clinically meaningful differences between products and add significantly to the overall
510 demonstration of biosimilarity. Using broader panels of biomarkers (e.g., by conducting a
511 protein or mRNA microarray analysis) that capture multiple pharmacological effects of the
512 product may be of additional value.

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514 When available and appropriate, clinical endpoints in clinical pharmacology studies may also
515 provide useful information about the presence of clinically meaningful differences between two
516 products.

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H. Defining the Appropriate Pharmacodynamic Time Profile

The optimal sampling strategy for determining PD measures may differ from the strategy used for PK measures. For PK sampling, frequent sampling at early time points following product administration with decreased frequency later is generally most effective to characterize the concentration-time profile. However, the PD-time profile may not mirror the PK-time profile. In such cases, the PD sampling should be well justified. When both PK and PD data are to be obtained during a clinical pharmacology study, the sampling strategy should be optimized for both PK and PD measures.

I. Statistical Comparison of PK and PD Results

The assessment of clinical pharmacology similarity of a proposed biosimilar product and the reference product in PK and PD studies is based on statistical evaluation. The recommended clinical pharmacology similarity assessment relies on: (1) a criterion to allow the comparison, (2) a confidence interval for the criterion, and (3) an acceptable limit. FDA recommends that log-transformation of the exposure measures be performed before the statistical analysis. Sponsors should use an average equivalence statistical approach¹² to compare PK and PD parameters for both replicate and nonreplicate design studies. This approach involves a calculation of a 90% confidence interval for the ratio between the means of the parameters of the proposed biosimilar product and the reference product. To establish PK and/or PD similarity, the calculated confidence interval should fall within an acceptable limit. Selection of the confidence interval and the acceptable limits may vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio may be 80–125%; however, this is not a default range, and the sponsor should justify the limits selected for the proposed biosimilar product. There may be situations in which the results of the PK and/or PD study fall outside the pre-defined limits. Although such results may suggest existence of underlying differences between the proposed biosimilar product and the reference product that may preclude development under the 351(k) pathway, FDA encourages sponsors to analyze and explain such findings. If such differences do not translate into clinically meaningful differences and the safety, purity and potency of the product are not affected, it may be possible to continue development under the 351(k) pathway.

V. UTILITY OF SIMULATION TOOLS IN STUDY DESIGN AND DATA ANALYSIS

Modeling and simulation tools can be useful when designing a PK and/or PD study. For instance, such tools can contribute to the selection of an optimally informative dose or doses for evaluating PD similarity. When a biomarker-based comparison is used, it is preferable that the selected dose be on the steep portion of the dose-response curve of the reference product. Sponsors should provide data to support the claim that the selected dose is on the steep part of the dose-response curve and not on the plateau of the dose-response curve where it is not likely to result in observed differences between two products. Publicly available data for the dose (or

¹² See FDA's guidance for industry *Statistical Approaches to Establishing Bioequivalence*.

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563 exposure)-response relationship of the reference product can be analyzed using model-based
564 simulations to justify the dose selected for the PK and/or PD study.

565
566 If the exposure-response data for the reference product are not available, the sponsor may decide
567 to generate this information using a small study to determine an optimally informative dose (e.g.,
568 representing the ED₅₀ of the reference product). Such a study may involve evaluating PK/PD at
569 multiple dose levels (e.g., low, intermediate, and the highest approved dose) to obtain dose-
570 response and/or exposure-response data.¹³ Alternatively, when possible, sponsors can conduct a
571 similarity study between the reference product and the proposed biosimilar product with low,
572 intermediate, and the highest approved dose where a clear dose-response is observed. If multiple
573 doses are studied, PK/PD parameters such as EC₅₀, E_{max}, and slope of the concentration effect
574 relationship should be evaluated for similarity. Such studies would be useful for the
575 demonstration of PK, PK/PD, and PD similarity when the clinical pharmacology evaluation is
576 likely to be the major source of information to assess clinically meaningful differences. Publicly
577 available information on biomarker-clinical endpoint relationships accompanied with modeling
578 and simulation can also be used to define the acceptable limits for PD similarity.

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VI. CONCLUSION

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583 Clinical pharmacology studies play a critical role in the development of biosimilar products.
584 These studies are part of a stepwise process for demonstrating biosimilarity between a proposed
585 biosimilar product and the reference product and add to the *totality of the evidence* to support an
586 overall demonstration of biosimilarity between the proposed biosimilar product and the reference
587 product through the demonstration of no clinically meaningful differences. Data gathered from
588 clinical pharmacology studies may also support a selective and targeted approach to the design of
589 any necessary subsequent clinical studies to support a demonstration of biosimilarity.

¹³ For more, see FDA's guidance for industry *Topical Dermatologic Corticosteroids: In Vivo Bioequivalence*.

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Biological product: “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹⁴

Biosimilar or biosimilarity means that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”¹⁵

Fingerprint-like: a term to describe integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.

Reference product: the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application.¹⁶

Average equivalence: an approach to statistical analysis for pharmacokinetic measures, such as area under the curve (AUC) and peak concentration (C_{max}). It is based on the *two one-sided tests procedure* to determine whether the average values for the pharmacokinetic measures determined after administration of the Test (T) and Reference (R) products are comparable. This approach involves the calculation of a 90% confidence interval for the ratio of the log-transformed averages of the measures for the T and R products.

¹⁴ Section 351(i)(1) of the PHS Act.

¹⁵ Section 351(i)(2) of the PHS Act.

¹⁶ Section 351(i)(4) of the PHS Act.