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# Guidance for Industry

## Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

### *DRAFT GUIDANCE*

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For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

**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)**

**February 2012  
Biosimilarity**

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## Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
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*Contains Nonbinding Recommendations*

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**TABLE OF CONTENTS**

<b>I.</b>	<b>INTRODUCTION</b> .....	<b>1</b>
<b>II.</b>	<b>SCOPE</b> .....	<b>2</b>
<b>III.</b>	<b>BACKGROUND</b> .....	<b>3</b>
<b>IV.</b>	<b>COMPLEXITIES OF PROTEIN PRODUCTS</b> .....	<b>4</b>
	<b>A. Nature of Protein Products and Related Scientific Considerations</b> .....	<b>4</b>
	<b>B. Manufacturing Process Considerations</b> .....	<b>5</b>
<b>V.</b>	<b>U.S.-LICENSED REFERENCE PRODUCT AND OTHER COMPARATORS</b> .....	<b>6</b>
<b>VI.</b>	<b>APPROACHES TO DEVELOPING AND ASSESSING EVIDENCE TO DEMONSTRATE BIOSIMILARITY</b> .....	<b>6</b>
	<b>A. Using a Stepwise Approach to Demonstrate Biosimilarity</b> .....	<b>7</b>
	<b>B. Using a <i>Totality-of-the-Evidence</i> Approach to Assess a Demonstration of Biosimilarity</b> ..	<b>8</b>
<b>VII.</b>	<b>DEMONSTRATING BIOSIMILARITY</b> .....	<b>8</b>
	<b>A. Structural Analysis</b> .....	<b>8</b>
	<b>B. Functional Assays</b> .....	<b>10</b>
	<b>C. Animal Data</b> .....	<b>10</b>
	1. <i>Animal Toxicity Studies</i> .....	<b>11</b>
	2. <i>Inclusion of Animal PK and PD Measures</i> .....	<b>12</b>
	3. <i>Animal Immunogenicity Studies</i> .....	<b>12</b>
	<b>D. Clinical Studies – General Considerations</b> .....	<b>12</b>
	1. <i>Human Pharmacology Data</i> .....	<b>13</b>
	2. <i>Clinical Immunogenicity Assessment</i> .....	<b>14</b>
	3. <i>Clinical Safety and Effectiveness Data</i> .....	<b>16</b>
	4. <i>Clinical Study Design Issues</i> .....	<b>17</b>
	5. <i>Extrapolation of Clinical Data Across Indications</i> .....	<b>19</b>
<b>VIII.</b>	<b>POSTMARKETING SAFETY MONITORING CONSIDERATIONS</b> .....	<b>20</b>
<b>IX.</b>	<b>CONSULTATION WITH FDA</b> .....	<b>21</b>
	<b>ATTACHMENT: TERMINOLOGY</b> .....	<b>22</b>

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**Guidance for Industry<sup>1</sup>**

**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product**

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This guidance is intended to assist sponsors in demonstrating that a proposed therapeutic protein product (hereinafter “proposed product”<sup>2</sup>) is biosimilar to a reference product for purposes of the submission of a marketing application under section 351(k) of the Public Health Service Act (PHS Act).<sup>3</sup> The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) amends the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111-148) (Affordable Care Act)). Although the 351(k) pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations for demonstrating biosimilarity.

This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act. The guidances will address a broad range of issues, including:

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency).

Guidance documents are available on the CDER guidance 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 CDER guidance page.

<sup>2</sup> In section II (Scope) of this document, the term “proposed product” is also used to describe a product that is the subject of a New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

<sup>3</sup> The statutory definition of *biosimilar* and definitions of selected other terms used in this guidance are provided in the attachment titled “Terminology.”

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- 34 • Quality Considerations in Demonstrating Biosimilarity to a Reference Protein
- 35 Product
- 36 • Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- 37 • Biosimilars: Questions and Answers Regarding Implementation of the Biologics
- 38 Price Competition and Innovation Act of 2009
- 39

40 When applicable, references to information in these guidances are included in this guidance.

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

47

48

### **II. SCOPE**

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50

51 This guidance gives an overview of FDA’s approach to determining biosimilarity, consistent  
52 with a longstanding Agency approach to evaluation of scientific evidence.<sup>4</sup> FDA intends to  
53 consider the *totality of the evidence* provided by a sponsor to support a demonstration of  
54 biosimilarity, and recommends that sponsors use a stepwise approach in their development of  
55 biosimilar products. This guidance discusses important scientific considerations in  
56 demonstrating biosimilarity, including:

57

- 58 • A stepwise approach to demonstrating biosimilarity, which can include a  
59 comparison of the proposed product and the reference product with respect to  
60 structure, function, animal toxicity, human pharmacokinetics (PK) and  
61 pharmacodynamics (PD), clinical immunogenicity, and clinical safety and  
62 effectiveness
- 63 • The *totality-of-the-evidence* approach that FDA will use to review applications for  
64 biosimilar products
- 65 • General scientific principles in conducting comparative structural and functional  
66 analysis, animal testing, human PK and PD studies, clinical immunogenicity  
67 assessment, and clinical safety and effectiveness studies (including clinical study  
68 design issues)
- 69

70

70 Additional topics discussed include the following:

71

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<sup>4</sup> The guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) provides insight to the concept of the *totality-of-the-evidence* approach in a different context (i.e., considerations of both the quantity and quality of the evidence to support effectiveness for drugs and biological products). Some of the principles discussed in that guidance may also be relevant in the design of a development program to support a demonstration of biosimilarity.

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- 72           • Considerations of the complexities of therapeutic protein products when designing a  
73           biosimilar development program, including manufacturing process considerations
- 74           • Use of data derived from studies comparing a proposed product with a non-U.S.-  
75           licensed product
- 76           • Postmarketing safety monitoring considerations
- 77

78           This guidance applies to applications submitted under section 351(k) of the PHS Act. However,  
79           some scientific principles described in this guidance may be informative for the development of  
80           certain biological products under section 505(b)(2) of the FD&C Act.<sup>5</sup> Section 505(b)(2) of the  
81           FD&C Act and section 351(k) of the PHS Act are two separate statutory schemes. This guidance  
82           is not intended to describe any relationship between the standards for approval under these  
83           schemes.

84

85

### **III. BACKGROUND**

86

87

88           The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI  
89           Act creates an abbreviated licensure pathway for biological products demonstrated to be  
90           biosimilar to, or interchangeable with, a reference product. Section 351(k) of the PHS Act (42  
91           U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a  
92           proposed biosimilar product and an application or a supplement for a proposed interchangeable  
93           product. Section 351(i) of the PHS Act defines *biosimilarity* to mean “that the biological product  
94           is highly similar to the reference product notwithstanding minor differences in clinically inactive  
95           components” and that “there are no clinically meaningful differences between the biological  
96           product and the reference product in terms of the safety, purity, and potency of the product.”<sup>6</sup>  
97           The BPCI Act also amended the definition of biological product to include “protein (except any  
98           chemically synthesized polypeptide).”<sup>7</sup>

99

100           Under section 351(k) of the PHS Act, a proposed biological product that is demonstrated to be  
101           biosimilar to a reference product can rely on certain existing scientific knowledge about the  
102           safety, purity, and potency<sup>8</sup> of the reference product to support licensure. FDA will license a  
103           proposed biological product submitted under section 351(k) of the PHS Act if FDA “determines

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<sup>5</sup> A 505(b)(2) application is an 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 published literature). 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.

<sup>6</sup> Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

<sup>7</sup> Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.

<sup>8</sup> The standard for licensure of a biological product as “potent” under section 351(a) of the PHS Act has long been interpreted to include effectiveness (see 21 CFR 600.3(s) and guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*). In this guidance, we use the terms “safety and effectiveness” and “safety, purity, and potency” interchangeably in the discussions pertaining to biosimilar products.

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104 that the information submitted in the application . . . is sufficient to show that the biological  
105 product is biosimilar to the reference product . . .” and the 351(k) applicant (or other appropriate  
106 person) consents to an inspection of the facility that is the subject of the application (i.e., a  
107 facility in which the proposed biological product is manufactured, processed, packed, or held).<sup>9</sup>  
108

109 An application submitted under section 351(k) of the PHS Act must contain, among other things,  
110 information demonstrating that “the biological product is biosimilar to a reference product”  
111 based upon data derived from:<sup>10</sup>  
112

- 113 • Analytical studies that demonstrate that the biological product is highly similar to the  
114 reference product notwithstanding minor differences in clinically inactive components;
- 115 • Animal studies (including the assessment of toxicity); and
- 116 • A clinical study or studies (including the assessment of immunogenicity and  
117 pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety,  
118 purity, and potency in one or more appropriate conditions of use for which the reference  
119 product is licensed and intended to be used and for which licensure is sought for the  
120 biological product.

121  
122 The Agency has the discretion to determine that an element described above is unnecessary in a  
123 351(k) application.<sup>11</sup> FDA advises sponsors intending to develop biosimilar products to meet  
124 with FDA to present their product development plans and establish a schedule of milestones that  
125 will serve as landmarks for future discussions with the Agency. FDA anticipates that early  
126 discussions with FDA about product development plans and about the appropriate scientific  
127 justifications will facilitate biosimilar development.  
128  
129

### **IV. COMPLEXITIES OF PROTEIN PRODUCTS**

130  
131  
132 A sponsor should consider the complexities of protein products and related scientific issues when  
133 it designs a development program to support a demonstration of biosimilarity.  
134

#### **A. Nature of Protein Products and Related Scientific Considerations**

135  
136  
137 Unlike small molecule drugs, whose structure can usually be completely defined and entirely  
138 reproduced, proteins are typically more complex and are unlikely to be shown to be structurally  
139 identical to a reference product. Many potential differences in protein structure can arise.  
140 Because even minor structural differences (including certain changes in glycosylation patterns)  
141 can significantly affect a protein’s safety, purity, and/or potency, it is important to evaluate these  
142 differences.  
143

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<sup>9</sup> Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(3) of the PHS Act; section 351(a)(2)(C) of the PHS Act.

<sup>10</sup> Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I) of the PHS Act.

<sup>11</sup> Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(ii) of the PHS Act.

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144 In general, proteins can differ in at least three ways: (1) primary amino acid sequence; (2)  
145 modification to amino acids, such as sugar moieties (glycosylation) or other side chains; and (3)  
146 higher order structure (protein folding and protein-protein interactions). Modifications to amino  
147 acids may lead to heterogeneity and can be difficult to control. Protein modifications and higher  
148 order structure can be affected by environmental conditions, including formulation, light,  
149 temperature, moisture, packaging materials, container closure systems, and delivery device  
150 materials. Additionally, process-related impurities may increase the likelihood and/or the  
151 severity of an immune response to a protein product, and certain excipients may limit the ability  
152 to characterize the drug substance.

153  
154 Advances in analytical sciences enable some protein products to be extensively characterized  
155 with respect to their physico-chemical and biological properties, such as higher order structures  
156 and functional characteristics. These analytical methodologies have increasingly improved the  
157 ability to identify and characterize not only the drug substance of a protein product, but also  
158 excipients and product- and process-related impurities.

159  
160 Despite such significant improvements in analytical techniques, however, current analytical  
161 methodology may not be able to detect all relevant structural and functional differences between  
162 two proteins. Thus, as set forth in the PHS Act, data derived from analytical studies, animal  
163 studies, and a clinical study or studies are required to demonstrate biosimilarity unless FDA  
164 determines an element unnecessary.<sup>12</sup>

### **B. Manufacturing Process Considerations**

166  
167  
168 Different manufacturing processes may alter a protein product in a way that could affect the  
169 safety or effectiveness of the product. For example, differences in biological systems used to  
170 manufacture a protein product may cause different post-translational modifications, which in turn  
171 may affect the safety or effectiveness of the product. Thus, when the manufacturing process for  
172 a marketed protein product is changed, the application holder must assess the effects of the  
173 change and demonstrate through appropriate analytical testing, functional assays, and/or in some  
174 cases animal and/or clinical studies, that the change does not have an adverse effect on the  
175 identity, strength, quality, purity, or potency of the product as they relate to the safety or  
176 effectiveness of the product.<sup>13</sup> The International Conference on Harmonisation (ICH) guidance  
177 *Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their*  
178 *Manufacturing Process* describes scientific principles in the comparability assessment for  
179 manufacturing changes.

180  
181 Demonstrating that a proposed product is biosimilar to a reference product typically will be more  
182 complex than assessing the comparability of a product before and after manufacturing changes  
183 made by the same manufacturer. This is because a manufacturer who modifies its own  
184 manufacturing process has extensive knowledge and information about the product and the  
185 existing process, including established controls and acceptance parameters. In contrast, the  
186 manufacturer of a proposed product will likely have a different manufacturing process (e.g.,

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<sup>12</sup> Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I) of the PHS Act.

<sup>13</sup> See 21 CFR 601.12 and 21 CFR 314.70 for regulatory requirements for changes (including manufacturing changes) made to a licensed biologics license application (BLA) and an approved NDA, respectively.



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187 different cell line, raw materials, equipment, processes, process controls, and acceptance criteria)  
188 from that of the reference product and no direct knowledge of the manufacturing process for the  
189 reference product. Therefore, even though some of the scientific principles described in *ICH*  
190 *Q5E* may also apply in the demonstration of biosimilarity, in general, more data and information  
191 will be needed to establish biosimilarity than would be needed to establish that a manufacturer's  
192 post-manufacturing change product is comparable to the pre-manufacturing change product.

193  
194

### **V. U.S.-LICENSED REFERENCE PRODUCT AND OTHER COMPARATORS**

196

197 To obtain licensure of a proposed product under section 351(k) of the PHS Act, a sponsor must  
198 demonstrate that the proposed product is biosimilar to a single reference product that previously  
199 has been licensed by FDA.<sup>14</sup> In general, a sponsor needs to provide information to demonstrate  
200 biosimilarity based on data directly comparing the proposed product with the reference product.  
201 For example, analytical studies and at least one human PK and/or PD study intended to support a  
202 demonstration of biosimilarity for purposes of section 351(k) of the PHS Act must, as a scientific  
203 matter, include an adequate comparison to the reference product licensed under section 351(a).  
204 However, under certain circumstances, a sponsor may seek to use data derived from animal or  
205 clinical studies comparing a proposed product with a non-U.S.-licensed product to address, in  
206 part, the requirements under section 351(k)(2)(A) of the PHS Act. In such a case, the sponsor  
207 should provide adequate data or information to scientifically justify the relevance of this  
208 comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the  
209 U.S.-licensed reference product.<sup>15</sup> Sponsors are encouraged to discuss with FDA during the  
210 development program the adequacy of the scientific justification and bridge to the U.S.-licensed  
211 reference product; a final decision about such adequacy will be made by FDA during review of  
212 the 351(k) application.

213

214 For additional scientific considerations relating to bridging studies, please refer to ICH guidance  
215 *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data*.

216

217

### **VI. APPROACHES TO DEVELOPING AND ASSESSING EVIDENCE TO DEMONSTRATE BIOSIMILARITY**

218

219  
220  
221 As described in detail below, FDA recommends that sponsors use a stepwise approach to  
222 develop the evidence needed to demonstrate biosimilarity. This approach may also be applicable  
223 to biosimilar applications for other types of biological products. FDA intends to consider the  
224 *totality of the evidence* provided by a sponsor when the Agency evaluates the sponsor's  
225 demonstration of biosimilarity, consistent with a longstanding Agency approach to evaluating  
226 scientific evidence.<sup>16</sup>

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<sup>14</sup> Sections 7002(a)(2) and (b)(3) of the Affordable Care Act, adding sections 351(k), 351(i)(2), and 351(i)(4) of the PHS Act.

<sup>15</sup> For examples of issues that a sponsor may need to address, see draft guidance entitled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*.

<sup>16</sup> See footnote 4.

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### **A. Using a Stepwise Approach to Demonstrate Biosimilarity**

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229  
230 The purpose of a biosimilar development program is to support a demonstration of biosimilarity  
231 between a proposed product and a reference product including an assessment of the effects of  
232 any observed differences between the products, but not to independently establish the safety and  
233 effectiveness of the proposed product. FDA recommends that sponsors use a stepwise approach  
234 to developing the data and information needed to support a demonstration of biosimilarity. At  
235 each step, the sponsor should evaluate the extent to which there is residual uncertainty about the  
236 biosimilarity of the proposed product and identify next steps to try to address that uncertainty.  
237 Where possible, studies conducted should be designed to maximize their contribution to  
238 demonstrating biosimilarity. For example, a clinical immunogenicity study may also provide  
239 other useful information about the safety profile of the proposed product.  
240

241 The stepwise approach should start with extensive structural and functional characterization of  
242 both the proposed product and the reference product, which serves as the foundation of a  
243 biosimilar development program (sections VII.A and VII.B). The more comprehensive and  
244 robust the comparative structural and functional characterization – the extent to which these  
245 studies are able to identify (qualitatively or quantitatively) differences in relevant product  
246 attributes between the proposed product and reference product (including the drug substance,  
247 excipients, and impurities) – the more useful such characterization will be in determining what  
248 additional studies may be needed. For example, if rigorous structural and functional  
249 comparisons show minimal or no difference between the proposed product and the reference  
250 product, the stronger the scientific justification for a selective and targeted approach to animal  
251 and/or clinical testing to support a demonstration of biosimilarity. It may be useful to further  
252 quantify the similarity or differences between the two products using a meaningful *fingerprint-*  
253 *like* analysis algorithm that covers a large number of additional product attributes and their  
254 combinations with high sensitivity using orthogonal methods. Such a strategy may further  
255 reduce the possibility of undetected structural differences between the products and lead to a  
256 more selective and targeted approach to animal and/or clinical testing. A sufficient  
257 understanding of the mechanism of action (MOA) of the drug substance and clinical relevance of  
258 any observed structural differences, clinical knowledge of the reference product and its class  
259 indicating that the overall safety risks are low, and the availability of a clinically relevant PD  
260 measure may provide further scientific justification for a selective and targeted approach to  
261 animal and/or clinical studies.  
262

263 The sponsor should then consider the role of animal data in assessing toxicity and, in some cases,  
264 in providing additional support for demonstrating biosimilarity and in contributing to the  
265 immunogenicity assessment (section VII.C). The sponsor should then conduct comparative  
266 human PK studies, and PD studies if there is a clinically relevant PD measure, in an appropriate  
267 study population (section VII.D.1). Sponsors should then compare the clinical immunogenicity  
268 of the two products (section VII.D.2). If there are residual uncertainties about the biosimilarity  
269 of the two products after conducting structural and functional studies, animal toxicity studies,  
270 human PK and PD studies, and clinical immunogenicity assessment, the sponsor should then  
271 consider what comparative clinical safety and effectiveness data may be adequate (section  
272 VII.D.3). FDA encourages sponsors to consult extensively with the Agency after completion of

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273 comparative structural and functional analysis (before finalizing the clinical program), and  
274 throughout development as needed.

275

### **B. Using a *Totality-of-the-Evidence* Approach to Assess a Demonstration of Biosimilarity**

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278  
279 In evaluating a sponsor's demonstration of biosimilarity, FDA will consider the totality of the  
280 data and information submitted in the application, including structural and functional  
281 characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data,  
282 and clinical safety and effectiveness data. FDA intends to use a risk-based, *totality-of-the-*  
283 *evidence* approach to evaluate all available data and information submitted in support of the  
284 biosimilarity of the proposed product.

285

286 A sponsor may be able to demonstrate biosimilarity even though there are formulation or minor  
287 structural differences, provided that the sponsor provides sufficient data and information  
288 demonstrating that the differences are not clinically meaningful and the proposed product  
289 otherwise meets the statutory criteria for biosimilarity. For example, differences in certain post-  
290 translational modifications, or differences in certain excipients (e.g., human serum albumin)  
291 might not preclude a finding of biosimilarity if data and information provided by the sponsor  
292 show that the proposed product is highly similar to the reference product notwithstanding minor  
293 differences in clinically inactive components and that there are no clinically meaningful  
294 differences between the products in terms of safety, purity, and potency.<sup>17</sup> Clinically meaningful  
295 differences could include a difference in the expected range of safety, purity, and potency of the  
296 proposed and reference products. By contrast, slight differences in rates of occurrence of  
297 adverse events between the two products ordinarily would not be considered clinically  
298 meaningful differences.

299

300

## **VII. DEMONSTRATING BIOSIMILARITY**

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302  
303 This section discusses scientific considerations in the stepwise approach to developing data and  
304 information needed to support a demonstration of biosimilarity. Although this guidance focuses  
305 on proposed biosimilar therapeutic protein products, the scientific principles discussed may also  
306 apply to other types of proposed biosimilar biological products. To demonstrate biosimilarity, a  
307 sponsor must provide sufficient data and information to show that the proposed product and the  
308 reference product are highly similar notwithstanding minor differences in clinically inactive  
309 components and that there are no clinically meaningful differences between the two products in  
310 terms of safety, purity, and potency.<sup>18</sup> The type and amount of analyses and testing that will be  
311 sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

312

### **A. Structural Analysis**

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<sup>17</sup> In this example, because some excipients may affect the ability to characterize products, a sponsor should provide evidence that the excipients used in the reference product will not affect the ability to characterize and compare the products.

<sup>18</sup> Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

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315 The PHS Act requires that a 351(k) application include information demonstrating biosimilarity  
316 based on data derived from, among other things, analytical studies that demonstrate that the  
317 biological product is highly similar to the reference product notwithstanding minor differences in  
318 clinically inactive components, unless FDA determines that an element is unnecessary in a  
319 351(k) application.<sup>19</sup> FDA expects that a sponsor first will extensively characterize the proposed  
320 product and reference product with state-of-the-art technology, because extensive  
321 characterization of both products serves as the foundation for a demonstration of biosimilarity.  
322 In general, FDA expects that the expression construct for a proposed product will encode the  
323 same primary amino acid sequence as the reference product. However, minor modifications  
324 such as N- or C-terminal truncations that will not affect safety and effectiveness may be justified  
325 and should be explained by the sponsor. Additionally, sponsors should consider all relevant  
326 characteristics of the proposed product (e.g., the primary, secondary, tertiary, and quaternary  
327 structure; post-translational modifications; and biological activities) to demonstrate that the  
328 proposed product is highly similar to the reference product notwithstanding minor differences in  
329 clinically inactive components. The more comprehensive and robust the comparative structural  
330 and functional characterization are, the stronger the scientific justification for a selective and  
331 targeted approach to animal and/or clinical testing.

332  
333 Sponsors should use an appropriate analytical methodology with adequate sensitivity and  
334 specificity for structural characterization of the proteins. Generally, such tests include the  
335 following comparisons of the drug substances of the proposed product and reference product:

- 336  
337
- Primary structures, such as amino acid sequence
  - 338 • Higher order structures, including secondary, tertiary, and quaternary structure  
339 (including aggregation)
  - 340 • Enzymatic post-translational modifications, such as glycosylation and  
341 phosphorylation
  - 342 • Other potential variants, such as protein deamidation and oxidation
  - 343 • Intentional chemical modifications, such as PEGylation sites and characteristics
- 344

345 Sponsors should conduct extensive structural characterization in multiple representative lots of  
346 the proposed product and the reference product to understand the lot-to-lot variability of both  
347 drug substances in the manufacturing processes. Lots used for the analysis should support the  
348 biosimilarity of both the clinical material used in confirmatory clinical trials and the to-be-  
349 marketed proposed product. Sponsors should justify the selection of the representative lots,  
350 including the number of lots.

351  
352 In addition, FDA recommends that sponsors analyze the finished dosage form of multiple lots of  
353 the proposed product and the reference product, assessing excipients and any formulation effect  
354 on purity, product- and process-related impurities, and stability. Differences in formulation

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<sup>19</sup> Section 7002(a)(2) of the Affordable Care Act, adding sections 351(k)(2)(A)(i)(I)(bb) and 351(k)(2)(A)(ii) of the PHS Act.

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355 between the proposed product and the reference product are among the factors that may affect  
356 the extent and nature of subsequent animal or clinical testing.<sup>20</sup>

357  
358 If the reference product cannot be adequately characterized with state-of-the-art technology, the  
359 sponsor should consult FDA for guidance on whether an application for such a protein product is  
360 appropriate for submission under section 351(k) of the PHS Act.

361

### **B. Functional Assays**

362

363  
364 The pharmacologic activity of protein products can be evaluated by in vitro and/or in vivo  
365 functional assays. These assays may include, but are not limited to, bioassays, biological assays,  
366 binding assays, and enzyme kinetics. A functional evaluation comparing a proposed product to  
367 the reference product using these types of assays is also an important part of the foundation that  
368 supports a demonstration of biosimilarity and may be used to scientifically justify a selective and  
369 targeted approach to animal and/or clinical testing.

370

371 Sponsors can use functional assays to provide additional evidence that the biologic activity and  
372 potency of the proposed product are highly similar to those of the reference product and/or to  
373 demonstrate that there are no clinically meaningful differences between the proposed product  
374 and the reference product. Such assays also may be used to provide additional evidence that the  
375 MOA of the two products is the same to the extent the MOA of the reference product is known.  
376 Functional assays can be used to provide additional data to support results from structural  
377 analysis, investigate the consequences of observed structural differences, and explore structure-  
378 activity relationships.<sup>21</sup> To be useful, these assays should be comparative, so they can provide  
379 evidence of similarity, or reveal differences, in the performance of the proposed product  
380 compared to the reference product, especially differences resulting from structural variations that  
381 cannot be detected using current analytical methods. FDA also recommends that sponsors  
382 discuss limitations of the assays they used when interpreting results in their submissions to the  
383 FDA.

384

385 Functional assays can also provide information that complements the animal and clinical data in  
386 assessing the potential clinical effects of minor differences in structure between the proposed  
387 product and reference product. For example, cell-based bioactivity assays can be used to detect  
388 the potential for inducing cytokine release syndrome in vivo. The available information about  
389 these assays, including sensitivity, specificity, and extent of validation, can affect the amount and  
390 type of additional animal or clinical data that may be needed to establish biosimilarity. As for  
391 the structural evaluation, appropriate lots should be used in the analysis.

392

### **C. Animal Data**

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<sup>20</sup> See also draft guidance entitled *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*.

<sup>21</sup> See also draft guidance entitled *Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product*.

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395 The PHS Act also requires that a 351(k) application include information demonstrating  
396 biosimilarity based on data derived from animal studies (including the assessment of toxicity),  
397 unless FDA determines that such studies are not necessary in a 351(k) application.<sup>22</sup>  
398

### 399 1. *Animal Toxicity Studies*

400  
401 As a scientific matter, animal toxicity data are considered useful when, based on the  
402 results of extensive structural and functional characterization, uncertainties remain about  
403 the safety of the proposed product that need to be addressed before initiation of clinical  
404 studies in humans. Animal toxicity studies are generally not useful if there is no animal  
405 species that can provide pharmacologically relevant data for the protein product (i.e., no  
406 species in which the biologic activity of the protein product mimics the human response).  
407 However, there may be some instances when animal data from a pharmacologically non-  
408 responsive species (including rodents) may be useful to support clinical studies with a  
409 proposed product that has not been previously tested in human subjects, for example  
410 comparative PK and systemic tolerability studies. For a more detailed discussion about  
411 demonstrating species relevance, see the criteria described in the ICH S6 guidance  
412 addendum *ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived*  
413 *Pharmaceuticals*.

414  
415 The scope and extent of any animal toxicity studies will depend on the body of  
416 information available on the reference product, the proposed product, and the extent of  
417 known similarities or differences between the two. If animal toxicity studies are not  
418 warranted, additional comparative in vitro testing, using human cells or tissues when  
419 appropriate, may be warranted. As described further in section IX, FDA encourages  
420 sponsors to initiate early discussions with the Agency with regard to their biosimilar  
421 development plans, including identifying appropriate scientific justifications for not  
422 conducting an animal toxicity study or the scope and extent of such a study.  
423

424 When animal toxicity studies are conducted, it will generally be useful to perform a  
425 comparative animal toxicology study with the proposed product and reference product  
426 (i.e., comparative bridging toxicology studies). The selection of dose, regimen, duration,  
427 and test species for these studies should provide a meaningful toxicological comparison  
428 between the two products. It is important to understand the limitations of such animal  
429 studies (e.g., small sample size, intra-species variations) when interpreting results  
430 comparing the proposed product and the reference product. A sponsor may be able to  
431 provide a scientific justification for a stand-alone toxicology study using only the  
432 proposed product instead of a comparative toxicology study. For a more detailed  
433 discussion on the design of animal toxicology studies, see *ICH S6/S6(R1)*.  
434

435 In general, nonclinical safety pharmacology, reproductive and developmental toxicity,  
436 and carcinogenicity studies are not warranted when the proposed product and reference  
437 product have been demonstrated to be highly similar through extensive structural and  
438 functional characterization and animal toxicity studies. If there are specific safety

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<sup>22</sup> Section 7002(a)(2) of the Affordable Care Act, adding sections 351(k)(2)(A)(i)(I)(bb) and 351(k)(2)(A)(ii) of the PHS Act.

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439 concerns based on the clinical use of the reference product, some of or all such additional  
440 animal studies with the proposed product may be warranted.

441

### 2. *Inclusion of Animal PK and PD Measures*

443

444 Under certain circumstances, a single-dose study in animals comparing the proposed  
445 product and reference product using PK and PD measures may contribute to the totality  
446 of evidence that supports a demonstration of biosimilarity. Specifically, sponsors can use  
447 results from animal studies to support the degree of similarity based on PK and PD  
448 profiles of the proposed product and the reference product. PK and PD measures also can  
449 be incorporated into a single animal toxicity study, where appropriate. Animal PK and  
450 PD assessment will not negate the need for human PK and PD studies.

451

### 3. *Animal Immunogenicity Studies*

453

454 Animal immunogenicity assessments generally do not predict potential immunogenic  
455 responses to protein products in humans. However, when differences in manufacturing  
456 (e.g., impurities or excipients) between the proposed product and the reference product  
457 may result in differences in immunogenicity, measurement of anti-protein antibody  
458 responses in animals may provide useful information relevant to patient safety.

459 Additionally, significant differences in the immune response profile in inbred strains of  
460 mice, for example, may indicate that the proposed product and the reference product  
461 differ in one or more product attributes not captured by other analytical methods. If  
462 available, this information is of value in the design of clinical immunogenicity  
463 assessment.

464

## **D. Clinical Studies – General Considerations**

466

467 The sponsor of a proposed product must include in its submission to FDA information  
468 demonstrating that “there are no clinically meaningful differences between the biological product  
469 and the reference product in terms of the safety, purity, and potency of the product.”<sup>23</sup>

470

471 In general, the clinical program for a 351(k) application must include a clinical study or studies  
472 (including an assessment of immunogenicity and PK or PD) sufficient to demonstrate safety,  
473 purity, and potency in one or more appropriate conditions of use for which the reference product  
474 is licensed and intended to be used and for which licensure is sought for the biological product,  
475 as set forth in the PHS Act.<sup>24</sup> The scope and magnitude of clinical studies will depend on the  
476 extent of residual uncertainty about the biosimilarity of the two products after conducting  
477 structural and functional characterization and possible animal studies. The frequency and  
478 severity of safety risks and other safety and effectiveness concerns for the reference product may  
479 also affect the design of the clinical program. Lessening the number or narrowing the scope of  
480 any of these types of clinical studies (i.e., human PK, PD, clinical immunogenicity, or clinical  
481 safety and effectiveness) should be scientifically justified by the sponsor.

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<sup>23</sup> Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2)(B) of the PHS Act.

<sup>24</sup> Section 7002(a)(2) of the Affordable Care Act, adding section 351(k)(2)(A)(i)(I)(cc) of the PHS Act.

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### *1. Human Pharmacology Data*

Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity. We have determined that both PK and PD studies (where there is a relevant PD measure) generally will be expected to establish biosimilarity, unless a sponsor can scientifically justify that an element is unnecessary.<sup>25</sup>

Human PK and PD profiles of a protein product often cannot be adequately predicted from functional assays and/or animal studies alone. Therefore, comparative human PK studies and, if clinically relevant PD measures are available, comparative human PD studies would be expected, unless a sponsor can provide a scientific justification that such studies are unnecessary. In addition, a human PK study that demonstrates similar exposure (e.g., serum concentration over time) with the proposed product and reference product can provide support for a biosimilarity demonstration. For example, a human PK study can be particularly useful when the exposure correlates to clinical safety and effectiveness. A human PD study that demonstrates a similar effect on a clinically relevant PD measure or measures related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) can also provide strong support for a biosimilarity determination.

Sponsors should provide a scientific justification for the selection of the human PK and PD study population (e.g., patients versus healthy subjects) and parameters, taking into consideration the relevance of such population and parameters, the population and parameters studied for the licensure for the reference product, as well as the current knowledge of the intra-subject and inter-subject variability of human PK and PD for the reference product. For example, FDA recommends that, to the extent possible, the sponsor select PD measures that (1) are relevant to clinical outcomes (e.g., on mechanistic path of MOA or disease process related to effectiveness or safety); (2) can be assessed after a sufficient period of time after dosing, and with appropriate precision; and (3) have the sensitivity to detect clinically meaningful differences between the proposed product and reference product. Sponsors should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity. Establishing a similar human PK and PD profile contributes to the demonstration of biosimilarity and may provide a scientific basis for a selective and targeted approach to subsequent clinical testing. Demonstrating that the proposed product and reference product have similar effects on a PD measure that is known to be clinically related to

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<sup>25</sup> PK and PD studies provide quite different types of information. In simple terms, a PK study measures how the body acts on a drug – how the drug is absorbed, distributed, metabolized, and eliminated, and a PD study measures how the drug acts on the body – typically assessing a measure or measures related to the drug’s biochemical and physiologic effects on the body. Therefore one type of study does not duplicate or substitute for the information provided by the other. Both PK studies and PD studies provide important information for assessing biosimilarity and therefore, as a scientific matter, comparative human PK studies and PD studies (where there is a relevant PD measure) generally will be expected.



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520 safety or effectiveness can provide further support for a selective and targeted approach  
521 to clinical safety/effectiveness studies. In certain circumstances, human PK and PD data  
522 may provide sufficient clinical data to support a demonstration of biosimilarity.

523  
524 The list provided below in section VII.D.3 (Clinical Safety and Effectiveness Data)  
525 includes some of the factors that can affect the ability of the human PK and PD studies to  
526 support a selective and targeted approach to the clinical program, and contribute to a  
527 demonstration of biosimilarity. Such factors also include whether the human PK and PD  
528 studies have used (1) clinically relevant PK and PD parameters (multiple PD measures  
529 that assess different domains of activities may be of value); (2) populations, dose(s), and  
530 route of administration that are the most sensitive to detect differences in PK and PD  
531 profiles; and (3) sensitive and relevant assays.

### 532 533 2. *Clinical Immunogenicity Assessment*

534  
535 The goal of the clinical immunogenicity assessment is to evaluate potential differences  
536 between the proposed product and the reference product in the incidence and severity of  
537 human immune responses. Immune responses may affect both the safety and  
538 effectiveness of the product by, for example, altering PK, inducing anaphylaxis, or  
539 promoting development of neutralizing antibodies that neutralize the product as well as  
540 its endogenous protein counterpart. Thus, establishing that there are no clinically  
541 meaningful differences in immune response between a proposed product and the  
542 reference product is a key element in the demonstration of biosimilarity. Structural,  
543 functional, and animal data<sup>26</sup> are generally not adequate to predict immunogenicity in  
544 humans. Therefore, at least one clinical study that includes a comparison of the  
545 immunogenicity of the proposed product to that of the reference product will generally be  
546 expected.

547  
548 The extent and timing (e.g., premarket testing versus pre- and postmarket testing) of a  
549 clinical immunogenicity program will vary depending on a range of factors, including the  
550 extent of analytical similarity between the proposed product and the reference product,  
551 and the incidence and clinical consequences of immune responses for the reference  
552 product. For example, if the clinical consequence is severe (e.g., when the reference  
553 product is a therapeutic counterpart of an endogenous protein with a critical, non-  
554 redundant biological function or is known to provoke anaphylaxis), more extensive  
555 immunogenicity assessments will likely be needed. If the immune response to the  
556 reference product is rare, two separate studies may be sufficient to evaluate  
557 immunogenicity: (1) a premarket study powered to detect major differences in immune  
558 responses between the two products and (2) a postmarket study designed to detect more  
559 subtle differences in immunogenicity.

560  
561 The overall design of immunogenicity studies will consider both the severity of  
562 consequences and the incidence of immune responses. FDA recommends use of a  
563 comparative parallel design (i.e., a head-to-head study) to assess potential differences in  
564 the risk of immunogenicity and support appropriate labeling. As discussed in section

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<sup>26</sup> Section VII.C.3 contains a discussion concerning animal immunogenicity studies.

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*Draft — Not for Implementation*

565 VII.D.4, it is generally only important to demonstrate that the immunogenicity of the  
566 proposed product is not increased, so a one-sided design will ordinarily be adequate to  
567 compare clinical immunogenicity of the proposed product and reference product.  
568 Acceptable differences in incidence and other immune response parameters should be  
569 discussed with the FDA in advance of the study. Differences in immune responses  
570 between a proposed product and the reference product in the absence of observed clinical  
571 sequelae may be of concern and may warrant further evaluation to assess whether there  
572 are clinically meaningful differences between the proposed product and the reference  
573 product.

574  
575 The study population used to compare immunogenicity should be justified and agreed to  
576 by the Agency. If a sponsor is seeking to extrapolate immunogenicity findings for one  
577 indication to other indications, the sponsor should consider using the study population  
578 and treatment regimen that are the most sensitive for detecting a difference in immune  
579 responses. Most often, this will be the population and regimen for the reference product  
580 for which development of immune responses with adverse outcomes is most likely to  
581 occur (e.g., patients with autoimmune diseases would be more likely to develop immune  
582 responses than patients with malignancies).

583  
584 The selection of clinical immunogenicity endpoints or PD measures associated with  
585 immune responses to therapeutic protein products (e.g., antibody formation and cytokine  
586 levels) should take into consideration the immunogenicity issues that have emerged  
587 during the use of the reference product. Sponsors should prospectively define the clinical  
588 immune response criteria (e.g., definitions of significant clinical events), using  
589 established criteria where available, for each type of potential immune response and  
590 obtain agreement from FDA on these criteria before initiating the study.

591  
592 The follow-up period should be determined based on (1) the time course for the  
593 generation of immune responses (such as the development of neutralizing antibodies,  
594 cell-mediated immune responses), and expected clinical sequelae (informed by  
595 experience with the reference product), (2) the time course of disappearance of the  
596 immune responses and clinical sequelae following cessation of therapy, and (3) the length  
597 of administration of the product. For example, the minimal follow-up period for  
598 chronically administered agents should be one year, unless a shorter duration can be  
599 justified by the sponsor.

600  
601 As a scientific matter, it is expected that the following will be assessed in clinical  
602 immunogenicity studies:

- 603
- 604 • Binding antibody: titer, specificity, relevant isotype distribution, time course of  
605 development, persistence, disappearance, and association with clinical sequelae
  
  - 606 • Neutralizing antibody: all of the above, plus neutralizing capacity to all relevant  
607 functions (e.g., uptake and catalytic activity, neutralization for replacement enzyme  
608 therapeutics)
- 609

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610 The sponsor should develop assays capable of sensitively detecting immune responses,  
611 even in the presence of circulating drug product (proposed product and reference  
612 product).<sup>27</sup> The proposed product and reference product should be assessed in the same  
613 assay with the same patient sera whenever possible. FDA recommends that  
614 immunogenicity assays be developed and validated with respect to both the proposed  
615 product and reference product early in development. Sponsors should consult with FDA  
616 on the sufficiency of assays before initiating any clinical immunogenicity study.

617

### 618 3. *Clinical Safety and Effectiveness Data*

619

620 As a scientific matter, comparative safety and effectiveness data will be necessary to  
621 support a demonstration of biosimilarity if there are residual uncertainties about the  
622 biosimilarity of the two products based on structural and functional characterization,  
623 animal testing, human PK and PD data, and clinical immunogenicity assessment. A  
624 sponsor may provide a scientific justification if it believes that some or all of these  
625 comparisons on clinical safety and effectiveness are not necessary.

626

627 The following are examples of factors that may influence the type and extent of the  
628 comparative clinical safety and effectiveness data needed.

629

- 630 1. The nature and complexity of the reference product, the extensiveness of structural  
631 and functional characterization, and the findings and limitations of comparative  
632 structural, functional, and nonclinical testing, including the extent of observed  
633 differences
- 634 2. The extent to which differences in structure, function and nonclinical pharmacology  
635 and toxicology predict differences in clinical outcomes, as well as the degree of  
636 understanding of the MOA of the reference product and disease pathology
- 637 3. The extent to which human PK or PD predicts clinical outcomes (e.g., PD measures  
638 known to be clinically relevant to effectiveness)
- 639 4. The extent of clinical experience with the reference product and its therapeutic class,  
640 including the safety and risk/benefit profile (e.g., whether there is a low potential for  
641 off-target adverse events), and appropriate endpoints and biomarkers for safety and  
642 effectiveness (e.g., availability of established, sensitive clinical endpoints)
- 643 5. The extent of any clinical experience with the proposed product

644 Sponsors should provide a scientific justification for how it intends to integrate these  
645 factors to determine whether and what types of clinical trials are needed and the design of  
646 any necessary trials. For example, if comparative clinical trials (using an equivalence or  
647 a non-inferiority design) are needed, these factors are also relevant to determining the  
648 equivalence or non-inferiority margin.

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<sup>27</sup> See draft guidance entitled *Assay Development for Immunogenicity Testing of Therapeutic Proteins* for more detailed discussion.

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649  
650 Additionally, specific safety or effectiveness concerns regarding the reference product  
651 and its class (including history of manufacturing- or source-related adverse events) may  
652 warrant more comparative clinical safety and effectiveness data. Alternatively, if the  
653 reference product has a long, relatively safe marketing history and there have been  
654 multiple versions of the reference product on the market with no apparent differences in  
655 clinical safety and effectiveness profiles, there may be a basis for a selective and targeted  
656 approach to the clinical program.

### 657 658 4. *Clinical Study Design Issues*

659  
660 Clinical studies should be designed such that they can demonstrate that the proposed  
661 product has neither decreased nor increased activity compared to the reference product.  
662 Decreased activity ordinarily would preclude licensure of a proposed product. Increased  
663 activity might be associated with more adverse effects, or might suggest that the proposed  
664 product should be treated as an entirely different product with superior efficacy, in which  
665 case the appropriate licensure pathway would be section 351(a) of the PHS Act. A study  
666 employing a two-sided test in which the null hypothesis is that either (1) the proposed  
667 product is inferior to the reference product or (2) the proposed product is superior to the  
668 reference product based on a pre-specified equivalence margin is the most  
669 straightforward study design for accomplishing this objective. The margins should be  
670 scientifically justified and adequate to enable the detection of clinically meaningful  
671 differences in effectiveness and safety between the proposed product and the reference  
672 product. A sponsor should use clinical knowledge about the reference product and its  
673 therapeutic class to establish an appropriate equivalence margin. Although the upper  
674 (superiority) and lower (inferiority) bounds of the margin will usually be the same, there  
675 may be cases in which a different upper and lower bound may be appropriate.

676  
677 In some cases, a one-sided test – non-inferiority design – may be appropriate for  
678 comparing safety and effectiveness and also advantageous as it would generally allow for  
679 a smaller sample size than an equivalence (two-sided) design. For example, if it is well-  
680 established that doses of the reference product higher than are recommended in its  
681 labeling do not create safety concerns, a one-sided test may be sufficient for comparing  
682 the efficacy of certain protein products (e.g., those products that pharmacodynamically  
683 saturate the target at some level and are used at or near the maximal level of clinical  
684 effect). Because it is generally important to demonstrate that a proposed product has no  
685 more risk in terms of safety and immunogenicity compared to a reference product, a one-  
686 sided test may also be adequate in a clinical study evaluating immunogenicity or other  
687 safety endpoints as long as it is clear that lower immunogenic or other adverse events  
688 would not have implications for the effectiveness of a protein product. A non-inferiority  
689 margin should also be scientifically based and pre-specified.<sup>28</sup>

690  
691 FDA recommends that sponsors provide a scientific justification for the proposed size  
692 and length of their clinical trials to allow for: (1) sufficient exposure to the proposed

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<sup>28</sup> A draft guidance entitled *Non-inferiority Clinical Trials* contains a discussion on choosing the non-inferiority margin.

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*Draft — Not for Implementation*

693 product and reference product; (2) the detection of relevant safety signals (including  
694 immunogenic responses), except for rare events or those that require prolonged exposure;  
695 and (3) the detection of clinically meaningful differences in effectiveness and safety  
696 between the two products. The size of the clinical trials also may be influenced by the  
697 specific treatment effect(s) and the effect size of the reference product, as well as the size  
698 of the disease population.

699  
700 FDA recommends that sponsors consider the use of population pharmacokinetics (PPK)  
701 to explain observed differences in safety and effectiveness that may occur due to  
702 variability in PK. PPK methods are described in the guidance for industry on *Population*  
703 *Pharmacokinetics* and involve the collection of only a few blood samples per patient.  
704 PPK methods are an efficient way to quantitate the influence of covariates (e.g., age or  
705 renal function) on PK and, in some cases, PD. Sponsors should consult the PPK  
706 guidance, in particular the discussion concerning the design of PPK studies to ensure the  
707 validity of the study results.

708  
709 FDA recommends that a sponsor use endpoints and study populations that will be  
710 clinically relevant and sensitive in detecting clinically meaningful differences in safety  
711 and effectiveness between the proposed product and reference product. A sponsor can  
712 use endpoints that are different from those in the reference product's clinical trials if they  
713 are scientifically justified. For example, certain endpoints (such as PD measures) are  
714 more sensitive than clinical endpoints and, therefore, may enable more precise  
715 comparisons of relevant therapeutic effects (e.g., international normalized ratio, or INR,  
716 is more sensitive to anticoagulant comparisons than the incidence of cerebral bleeds or  
717 stroke). There may be situations when multiple PD measures enhance the sensitivity of a  
718 study. The adequacy of the endpoints also depends on the extent to which PD measures  
719 correlate with clinical outcome, the extent of structural and functional data support for  
720 biosimilarity, the understanding of MOA, and the nature or seriousness of outcome  
721 effected (risk of difference).

722  
723 When selecting the study population for a comparative safety and effectiveness study, a  
724 sponsor should consider, for example, whether its study population has characteristics  
725 consistent with those of the population studied for the licensure of the reference product  
726 for the same indication and whether patients have different co-morbidities and disease  
727 states (e.g., immuno-competent or immuno-suppressed) and receive different  
728 concomitant medications. In general, using similar study populations is essential for  
729 supporting the constancy assumption that is critical to interpreting the non-inferiority  
730 finding in a one- or two-sided comparative test.<sup>29</sup>

731  
732 For human PK and PD studies, FDA recommends use of a crossover design for products  
733 with a short half-life (e.g., shorter than five days) and low incidence of immunogenicity.  
734 For products with a longer half-life (e.g., more than five days), a parallel study will  
735 usually be needed. In addition, sponsors should provide a scientific justification for the  
736 selection of study subjects (e.g., healthy volunteers or patients), study dose (e.g., one dose

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<sup>29</sup> A draft guidance entitled *Non-inferiority Clinical Trials* contains a discussion on the constancy assumption.

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*Draft — Not for Implementation*

737 or multiple doses), route of administration, and sample size. FDA recommends that  
738 sponsors consider the duration of time it takes for a PD measure or biomarker to change,  
739 and the possibility of nonlinear PK caused by dose or PD. FDA also recommends  
740 consideration of the role of modeling and simulation in designing clinical studies on  
741 human PK or PD. When there are established dose-response or systemic exposure-  
742 response relationships (response may be PD measures or clinical endpoints), comparative  
743 exposure-response data can support a selective and targeted approach to clinical  
744 safety/effectiveness studies. It is important to select, whenever possible, doses for study  
745 on the steepest part (as opposed to the plateau) of the dose-response curve for the  
746 proposed product (see below), because even drugs with quite different potency will  
747 appear similar if the doses are studied on or near the plateau of a dose-response curve.  
748

749 Sponsors should consider the limitations of the clinical trial design and results. As noted,  
750 when the administered dose is on the plateau of a dose-response curve, the clinical trial  
751 will not be sensitive in detecting PD differences between the two products. In such a  
752 case, a sponsor should use lower doses if available and appropriate (e.g., known to have  
753 the same effect or ethically acceptable to give lower doses notwithstanding differences in  
754 effect), or a sponsor could use a study subgroup whose response is not on the plateau of  
755 the dose-response curve. A low efficacy rate (e.g.,  $\leq 25\%$ ) also may reduce the  
756 sensitivity of detecting product differences in patients in a clinical trial.  
757

### 5. *Extrapolation of Clinical Data Across Indications*

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760 If the proposed product meets the statutory requirements for licensure as a biosimilar  
761 product under section 351(k) of the PHS Act based on, among other things, data derived  
762 from a clinical study sufficient to demonstrate safety, purity, and potency in an  
763 appropriate condition of use, the potential exists for the proposed product to be licensed  
764 for one or more additional conditions of use for which the reference product is licensed.  
765 However, the sponsor will need to provide sufficient scientific justification for  
766 extrapolating clinical data to support a determination of biosimilarity for each condition  
767 of use for which licensure is sought.  
768

769 Such scientific justification should address, for example, the following issues for the  
770 tested and extrapolated conditions of use.  
771

- 772 • The MOA(s) in each condition of use for which licensure is sought; this may  
773 include the following
  - 774 – The target/receptor(s) for each relevant activity/function of the product
  - 775 – The binding, dose/concentration response, and pattern of molecular signaling  
776 upon engagement of target/receptor(s)
  - 777 – The relationship between product structure and target/receptor interactions
  - 778 – The location and expression of the target/receptor(s)

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- 779           • The PK and bio-distribution of the product in different patient populations; PD  
780           measures may provide important information on the MOA
- 781           • Differences in expected toxicities in each condition of use and patient population  
782           (including whether expected toxicities are related to the pharmacological activity of  
783           the product or to off-target activities)
- 784           • Any other factor that may affect the safety or effectiveness of the product in each  
785           condition of use and patient population for which licensure is sought  
786

787           In choosing which condition of use to study that would permit subsequent extrapolation  
788           of clinical data to other conditions of use, FDA recommends that a sponsor consider  
789           whether the tested condition of use is the most sensitive one in detecting clinically  
790           meaningful differences in safety (including immunogenicity) and effectiveness. A  
791           sponsor should be cautious with respect to the extrapolation of safety risk profiles across  
792           indications, because patient populations for different indications may have different co-  
793           morbidities and receive different concomitant medications. The sponsor of a proposed  
794           product may seek licensure only for a condition of use that has been previously licensed  
795           for the reference product.  
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## **VIII. POSTMARKETING SAFETY MONITORING CONSIDERATIONS**

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800           Robust postmarketing safety monitoring is an important component in ensuring the safety and  
801           effectiveness of biological products, including biosimilar therapeutic protein products. Because  
802           some aspects of postmarketing safety monitoring are product-specific, FDA encourages sponsors  
803           to consult with appropriate FDA divisions to discuss the sponsors' proposed approach to  
804           postmarketing safety monitoring.  
805

806           Postmarketing safety monitoring should first take into consideration any particular safety or  
807           effectiveness concerns associated with the use of the reference product and its class, as well as  
808           the proposed product in its development and clinical use (if marketed outside the United States).  
809           Postmarketing safety monitoring for a proposed product should also have adequate mechanisms  
810           in place to differentiate between the adverse events associated with the proposed product and  
811           those associated with the reference product, including the identification of adverse events  
812           associated with the proposed product that have not been previously associated with the reference  
813           product. Rare, but potentially serious, safety risks (e.g., immunogenicity) may not be detected  
814           during preapproval clinical testing because the size of the population exposed likely will not be  
815           large enough to assess rare events. In particular cases, such risks may need to be evaluated  
816           through postmarketing surveillance or studies. In addition, like any other biological products,  
817           FDA may take any appropriate action to ensure the safety and effectiveness of a proposed  
818           product, including, for example, requiring a postmarketing study to evaluate certain safety  
819           risks.<sup>30</sup>  
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<sup>30</sup> See, e.g., sections 505(o)(3) and 505(p)(1)(A)(ii) of the FD&C Act.

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821 Labeling of a proposed product should include all the information necessary for a health  
822 professional to make prescribing decisions, including a clear statement advising that:

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- 824 • This product is approved as biosimilar to a reference product for stated  
825 indication(s) and route of administration(s).
  
  - 826 • This product (has or has not) been determined to be interchangeable with the  
827 reference product.
- 828

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### **IX. CONSULTATION WITH FDA**

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832 As discussed above, many product-specific factors can influence the components of a product  
833 development program intended to establish that a proposed product is biosimilar to a reference  
834 product. Therefore, FDA will ordinarily provide feedback on a case-by-case basis on the  
835 components of a development program for a proposed product. In addition, it may not be  
836 possible to identify in advance all the necessary components of a development program, and the  
837 assessment of one element (e.g., structural analysis) at one step can influence decisions about the  
838 type and amount of subsequent data for the next step. For these reasons, as indicated above,  
839 FDA recommends that sponsors use a stepwise procedure to establish the *totality of the evidence*  
840 that supports a demonstration of biosimilarity.

841

842 FDA also advises sponsors intending to develop biosimilar products to meet with FDA to present  
843 their product development plans and establish a schedule of milestones that will serve as  
844 landmarks for future discussions with the Agency. FDA anticipates that early discussions with  
845 FDA about product development plans and about the appropriate scientific justifications will  
846 facilitate biosimilar development.



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### ATTACHMENT: TERMINOLOGY

As used in this guidance, the following terms are defined below:

- *Biological product* means “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.”<sup>31</sup>
- *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.”<sup>32</sup>
- *Chemically synthesized polypeptide* means any alpha amino acid polymer that is a) made entirely by chemical synthesis and b) is less than 100 amino acids in size.
- *Product*, when used without modifiers in this guidance, is intended to refer to the intermediates, drug substance, and/or drug product, as appropriate. The use of the term “product” is consistent with the use of the term in *ICH Q5E*.
- *Protein* means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.
- *Reference product* means 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.<sup>33</sup>

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<sup>31</sup> Section 7002(b)(2) of the Affordable Care Act, amending section 351(i)(1) of the PHS Act.

<sup>32</sup> Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

<sup>33</sup> Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(4) of the PHS Act.