Biosimilars Litigation and Client Counseling

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FDA Approval and Regulatory Process*

Biological products—or "biologics"—meet the statutory definition of "drug" and thus are subject to strict regulation to ensure that a product both is safe to administer to and provides some therapeutic benefit for patients. The term "biologic" is broad, encompassing a wide range of products, including many of the newest cutting-edge technologies, and both new biological products and follow-on biologics, called "biosimilars," and their substitutable counterparts, "interchangeable biosimilars," fall under the biologic rubric. There are, however, very different licensing requirements for each type of biologic application. With those licensing requirements come certain data exclusivity and intellectual property considerations, which again differ depending on the type of biologic application, and which differ significantly from the parallel process for small molecules. Consequently, understanding the application process for biological products, the requirements for licensure, the related regulatory scheme for both new and biosimilars, and the available exclusivities is critical to understanding a client's needs and considerations with respect to the biosimilar litigation practice.

I. Background

Biologics fall under the purview of the U.S. Food and Drug Administration (FDA). FDA has authority to regulate any products that meet the definition of "drug," which includes both products that are subject to the Federal Food, Drug, and Cosmetic Act (FDC Act) and the Public Health Service Act (PHS Act).[1] The FDC Act defines the broader category of drugs as follows:

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1. Pub. L. No. 75-717, 52 Stat. 1040 (1938); Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (1944).

> (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).[2]

Any product meeting this definition is subject to FDA regulation under title 21 of the *Code of Federal Regulations*, which houses all of the regulations implementing the agency's governing statutes.

While FDA's general regulatory authority arises from the FDC Act, the PHS Act sets forth the agency's authority to regulate a subset of products that meet the FDC Act definition of "drug." Those drugs are known as "biological products" or "biologics," defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, 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."[3]

FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products.[4] These drugs are typically larger, more complex molecules than other drugs regulated by FDA and are made from living sources, like bacteria, yeast, and animal cells.[5] Because they are made from living sources, there often are many variations from batch to batch, rendering them more complicated to purify, process, and manufacture.[6] And because each variation can dramatically affect the characteristics of a given biologic, FDA regulates and licenses both the biological product itself, as well as its manufacturing process.

Rather than assess biologics for "safety and effectiveness," as it does for small-molecule drugs, FDA assesses biologics based on their safety,

2. 21 U.S.C. § 321(g).

3. 42 U.S.C. § 262(i).

4. *Frequently Asked Questions about Therapeutic Biological Products*, FDA, https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products (last updated July 7, 2015).

5. *Overview for Health Care Professionals*, FDA, https://www.fda.gov/drugs/biosimilars/overview-health-care-professionals (last updated Jan. 1, 2024).

6. *Id*.

purity, and potency.[7] To that end, biological products are evaluated and licensed by FDA on the basis of a demonstration that the biological product is, and the facility used in its manufacture meets standards to ensure that the product is, "safe, pure, and potent."[8] While not defined by statute, FDA regulations define each of these terms in turn. "Safety" is the "relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered."[9] "Purity" is defined as "relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product."[10] "Potency" is akin to efficacy, "interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."[11] FDA requires extensive data submitted in an application for licensure to assess safety, purity, and potency of both biologics and follow-on biosimilars.[12]

II. Types of Biological Products

As noted, the PHS Act defines "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, 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."[13] This definition has been integrated into FDA regulations, which provide more detail on each of the aforementioned types of biological product.[14]

At the outset, a product only meets the definition of a "biological product" if that product is "deemed *applicable to the prevention*, *treatment*, *or cure of diseases or injuries of man*."[15] FDA's implementing regulations explain that the mode of administration or application of the product is irrelevant; in other words, the product need not be specifically used to *treat* disease or injury. It can still be a biological product even if the product only is "intended . . . as an aid in diagnosis, or in evaluating the degree of

7. 42 U.S.C. § 262(a)(2).
8. *Id*.
9. 21 C.F.R. § 600.3(p) (2024).
10. *Id*. § 600.3(r).
11. *Id*. § 600.3(s).
12. 42 U.S.C. § 262(a)(2).
13. *Id*. § 262(i).
14. 21 C.F.R. § 600.3 (2024).
15. *Id*. § 600.3(j) (emphasis added).

susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis," assuming a biological product is used to either prepare or aid in the preparation of the diagnostic substance.[16]

Because the statutorily enumerated types of biological products are open to interpretation, FDA has adopted specific definitions of several of these types. Under FDA's implementing regulations:

- A *virus* is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.[17]
- A *therapeutic serum* is a product obtained from blood by removing the clot or clot components and the blood cells.[18]
- A *toxin* is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of nonfatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.[19]
- An *antitoxin* is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.[20]
- *Blood* means a product that is a fluid containing dissolved and suspended elements which was collected from the vascular system of a human.[21]
- *Blood component* means a product containing a part of blood separated by physical or mechanical means.[22]
- *Allergenic Products* are products that are administered to man for the diagnosis, prevention or treatment of allergies.[23]
- *Trivalent organic arsenicals* means arsphenamine and its derivatives (or any other trivalent organic arsenic

16. *Id*.
17. *Id*. § 600.3(h)(1) (emphasis added).
18. *Id*. § 600.3(h)(2) (emphasis added).
19. *Id*. § 600.3(h)(3) (emphasis added).
20. *Id*. § 600.3(h)(4) (emphasis added).
21. *Id*. § 630.3(a).
22. *Id*. § 630.3(b).
23. *Id*. § 680.1(a) (emphasis added).

> compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.[24]

FDA has not promulgated a regulatory definition of "vaccine," and while FDA has codified definitions of "protein" and "analogous product," these definitions are somewhat more complicated.

A. Protein

Until the passage of the Biologics Price Competition and Innovation Act (BPCIA)[25] in 2010, a "protein" could be regulated as either a small molecule under section 505 of the FDC Act (21 U.S.C. § 355) or section 351 of the PHS Act (42 U.S.C. § 262). Though the majority of proteins were licensed as biologics, the dividing line between drug or biologic was unclear.[26] With the BPCIA, lines were drawn, as Congress amended the definition of "biological product" specifically to include a "protein (except any chemically synthesized polypeptide)."[27] "Protein," in turn, was defined as "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."[28] In 2020, however, Congress removed the exception for chemically synthesized polypeptides, such that now *all* polypeptides with 40 or more amino acids, regardless of how they are made, are regulated as a biological product.[29]

The BPCIA provided a ten-year transition period during which proteins could be approved either under the FDC Act or the PHS Act unless FDA had already approved the proposed product under the PHS Act.[30] At the end of that ten-year period, all new drug applications (NDAs) for proteins approved under the FDC Act transitioned to biologics license applications (BLAs) approved under the PHS Act, called "deemed BLAs," and all new protein products were required to seek approval as biologics under a BLA pursuant to the PHS Act.[31]

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24. *Id*. § 600.3(h)(6)(i).

25. Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

26. *See* Definition of the Term "Biological Product," 85 Fed. Reg. 10,057, 10,058 (Feb. 21, 2020) ("The BPCI Act clarified the statutory authority under which certain protein products are to be regulated.").

27. Pub. L. No. 11-148, § 7002(b)(1).

28. Definition of the Term "Biological Product," 83 Fed. Reg. 63,817, 63,817 (proposed Dec. 12, 2018).

29. Further Consolidated Appropriations Act, Pub. L. No. 116-94, § 605, 133 Stat. 2534, 3127 (2019).

30. Pub. L. No. 11-148, § 7002(e)(1)–(3). If a molecule was already approved under the PHS Act, any application for the same molecule must have been filed under the PHS Act.

31. *Id*. § 7002(e)(4).

On March 23, 2020, that transition occurred and approximately 85 products previously approved under the FDC Act were "deemed" biologics.[32] That transition was not without issue, however. Several manufacturers sued FDA over its interpretation of the term "protein." Immediately after the transition date, Teva Pharmaceuticals Industries Ltd. and Teva Pharmaceuticals USA, Inc. sued FDA in the District Court of the District of Columbia challenging the agency's failure to transition its Copaxone (glatiramer acetate) to a deemed BLA on the transition date.[33] Teva argued that Copaxone meets the statutory definition of "biological product" given that the product is a chemically synthesized polypeptide with an average length of 40 to 100 amino acids. FDA, however, noted that the regulations define "protein" to have more than 40 amino acids in "specific, defined sequence"; because Copaxone does not have such a sequence, it could not be a protein, argued FDA.[34] The court deferred to FDA's interpretation.[35]

Three years later, Ipsen sued FDA over the same provision. This time, Ipsen argued that the agency's decision to regulate Ipsen's Somatuline Depot (lanreotide acetate) as a drug under the FDC Act rather than a biological product under the PHS Act was arbitrary and capricious because its *finished drug product* had more than 40 amino acids; in contrast, FDA made its assessment of "protein" based on the *active ingredient*.[36] A synthetic octapeptide available as ready-to-use prefilled syringes for deep subcutaneous injection, Somatuline Depot consists of only eight amino acids linked in a polypeptide chain, but it contains multiple copies of its active ingredient that are linked together "in a manner that occurs in nature" to form a "nanotube" greater than 40 amino acids long.[37] Ipsen argued that FDA should look to the nanotube—not the individual active ingredient—to determine whether a given product meets the 40 amino acid definition of "protein." FDA disagreed with Ipsen's approach to defining a protein and took the position that the finished product form (i.e., the nanotube) is irrelevant because it is the "active ingredient" that is the relevant peptide for consideration of a "protein." Because the active ingredient of Somatuline Depot is *not* the nanotube but is the eight amino acids linked in the polypeptide chain, FDA argued that Somatuline Depot is not a protein and is

32. FDA, List of Approved NDAs for Biological Products That Were Deemed to Be BLAs on March 23, 2020, https://www.fda.gov/media/119229/download.

33. Complaint, Teva Pharms. USA, Inc. v. FDA, No. 1:20-cv-00808 (D.D.C. Mar. 24, 2020), ECF No. 1.

34. Memorandum Opinion, Teva Pharms. USA, Inc. v. FDA, No. 1:20-cv-00808 (D.D.C. Dec. 31, 2020), ECF No. 54 [hereinafter Teva Opinion].

35. *Id*.

36. Memorandum Opinion, Ipsen Biopharms., Inc. v. Becerra, No. 1-22-cv-00860 (D.D.C. May 8, 2023), ECF No. 42 [hereinafter Ipsen Opinion].

37. *Id*.

appropriately regulated as a drug product under the FDC Act. Ultimately, the court agreed with FDA.

The court found that FDA's determination that Ipsen's Somatuline Depot is not a biologic was consistent with the regulation's plain language and reflects rational decision-making. The court explained that "neither the statute nor the regulatory definition of a 'protein' *requires* the FDA to consider the size of the active ingredient as it appears in the final drug product, rather than standing alone."[38] Instead, FDA's decision to assess the active ingredient based on what "confers [its] pharmacologic activity" "was unambiguously correct"—and even if it were not, the court stated it would "defer to the FDA's interpretation as reasonable" because it falls within FDA's area of special expertise.[39]

As a result of these two cases, a protein unambiguously requires the *active ingredient* to contain a *specific*, *defined sequence* of 40 or more amino acids.

B. Analogous Product

Finally, under FDA's implementing regulations, whether a product is "analogous" for purposes of determining whether it is a biologic depends on the type of product used as the comparator.[40] A product is analogous to a virus if it is "prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used."[41] It is analogous to a therapeutic serum "if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum."[42] If a product is intended to be analogous to a toxin or antitoxin, it must be, "irrespective of its source of origin," "applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process."[43]

FDA has not promulgated regulations describing what it means to be "analogous" to a "protein" and specifically did not do so when updating its regulations to include a definition of a "protein."[44] At that time, in response to a comment urging FDA to "propose a regulatory definition of products that are 'analogous' to a protein and therefore are biological products,"

38. *Id*. at 21.
39. *Id*. at 21, 23.
40. 21 C.F.R. § 600.3(h)(5) (2024).
41. *Id*. § 600.3(h)(5)(i).
42. *Id*. § 600.3(h)(5)(ii).
43. *Id*. § 600.3(h)(5)(iii).
44. Definition of the Term "Biological Product," 85 Fed. Reg. 10,057, 10,057 (Feb. 21, 2020).

FDA declined, noting that it was "outside the scope of this rulemaking."[45] All FDA said on the issue is that "it would not be appropriate for the statutory term 'analogous product' to be interpreted in a way that would include products that are specifically excluded by this final rule."[46]

With no definition of "analogous product" for proteins, the same litigation that challenged the meaning of the term "protein" also challenged FDA's *lack* of definition of an analogous protein. As arguments in the alternative (i.e., if the courts upheld FDA's determination that neither product met the definition of a protein), both Teva and Ipsen asserted that their products—a product without a "specific, defined sequence" and a nanotube with eight amino acids in repetition respectively—were "analogous" to a protein.[47] In both cases, FDA took the position that the products at issue could not be analogous to proteins because such an interpretation would include amino acid polymers that are specifically excluded by the interpretation of the term "protein" in FDA's final rule.[48]

The courts agreed with FDA: a product that was decisively *not a protein* could not be considered a protein under the "analogous" provision. In the Copaxone case, FDA stated that it "would not consider an amino acid polymer that does not have a specific, defined sequence to be 'analogous' to a protein."[49] Instead, FDA explained that the term "analogous" was intended to address substances and mixtures composed "at least in part of a protein with a specific, defined sequence" even if the "protein component" is in "low levels or unknown amounts."[50] The District Court for the District of Columbia distilled that explanation to mean that FDA "appears to understand the 'analogous product' category as a narrow residual provision" for products that satisfy the regulatory definitions of each category in *most* ways but are not an *exact* fit.[51] One example, the court cited, is a protein that includes one or more non-biological products that contribute to the product's activity.[52] Such products are "analogous" to proteins "because their protein components are 'necessary . . . to achieving the intended therapeutic effect,' but they are not simply 'proteins' because their non-biological product components also contribute to their efficacy."[53] In the case at hand, FDA determined that Copaxone does not contain any component with a "specific, defined sequence," and therefore it could not

45. *Id*. at 10,061.
46. *Id*.
47. Teva Opinion, *supra* note 34, at 20; Ipsen Opinion, *supra* note 36, at 27.
48. Teva Opinion, *supra* note 34, at 20.
49. *Id*. at 65.
50. *Id*. at 65–66.
51. *Id*. at 71–72.
52. *Id*. at 72.
53. *Id*.

be considered either a protein or "analogous" to one.[54] In turn, the court held that, though FDA's definition of the "analogous product" provision is "not well-defined or well-explained," the determination that an analogous protein must have a "specific, defined sequence" of amino acids is reasonable and thus could stand.[55]

In the case of Somatuline Depot, the District Court for the District of Columbia reiterated the same conclusion: "it would not be appropriate to interpret the statutory term . . . in a way that would include amino acid polymers that are specifically excluded by the interpretation of the term 'protein' set forth in FDA's [Biological Product Definition Final Rule]."[56] Thus, the court held that Somatuline Depot, based on its active ingredient with only eight amino acids, is "in no way comparable or 'analogous' to a protein, which is 40 or more amino acids in size."[57] Notably, in this case, Ipsen implicitly took the position that the term "analogous product" in the statute must be defined to include at least one product analogous to each and every discrete type of biological product in the statute. The court flatly rejected that position.[58]

While FDA has not clearly established what it means to be "analogous" to a protein, it has firmly established what it does not mean: if expressly excluded from the definition of protein, a product cannot be "analogous" to one.

III. Licensure of Biologics, Biosimilars, and Interchangeables

FDA licenses under the statute (or, more colloquially, approves) a given biological product pursuant to a BLA for a new product, often called a "reference product," or an abbreviated BLA (aBLA) for a biosimilar.[59] Biosimilars, in turn, can include both biosimilars, which are "highly similar" to a product licensed under a BLA, and "interchangeable" biosimilars, which have been demonstrated to be so similar to its reference product that it can be substituted for that product without the intervention of a health care provider.[60] Each has its own requirements for submission.

54. *Id*.
55. *Id*. at 67.
56. Ipsen Opinion, *supra* note 36, at 27.
57. *Id*. at 29–30.
58. *Id*.
59. 42 U.S.C. § 262(a), (k), (i)(4).
60. *Id*. § 262(i)(2), (3).

A. BLAs

Novel products that fall under the statutory definition of a "biological product," which became known as reference products after the passage of the BPCIA, require licensure of a BLA under section 351 of the PHS Act, which serves as a "request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce."[61] Pursuant to 21 C.F.R. § 601.2, a manufacturer must submit a BLA and all its requisite parts to FDA through its Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER) based on the type of product approval that is sought.[62] CDER has responsibility for monoclonal antibodies for in vivo use, cytokines, growth factors, enzymes, immunomodulators, thrombolytics, proteins intended for therapeutic use that are extracted from animals or microorganisms (including recombinant versions of these products with the exception of clotting factors), and other non-vaccine therapeutic immunotherapies. Other biological products, including blood products and vaccines, are the responsibility of CBER.[63]

In addition to administrative documents like an application form, a BLA must include all data necessary to demonstrate safety and potency of the proposed product. This includes data derived from nonclinical studies performed in accordance with FDA's requirement for Good Laboratory Practices[64] and clinical studies that demonstrate the proposed product is safe and effective.[65] FDA expects to see "substantial evidence of effectiveness" in order to support BLA licensure, which typically requires at least two adequate and well-controlled clinical investigations, which usually are conducted under an investigational new drug application (IND).[66] Financial certifications and/or disclosure statements for clinical investigators must be included as part of the BLA, and each human clinical study should comply with FDA regulations for institutional review and informed consent.[67]

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61. *Biologics License Applications (BLA) Process (CBER)*, FDA, https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber (last updated Jan. 27, 2021).

62. *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, FDA, https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research (last updated Mar. 7, 2022).

63. *Id*.

64. *See* 21 C.F.R. pt. 58 (2024).

65. *Id*. § 601.2(a).

66. FDA, Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products 4 (2019), https://www.fda.gov/media/133660/download.

67. 21 C.F.R. § 601.2(a) (2024); *see also id*. pt. 56; *id*. pt. 50.

Equally important as clinical studies demonstrating safety and potency is the Chemistry, Manufacturing, and Controls section of a BLA, which is used to assess purity. There, FDA requires the submission of a full description of all manufacturing methods, data establishing the stability of the product through the proposed dating period, summaries of testing results, and representative samples of the proposed product for introduction into interstate commerce.[68] BLAs must also include samples of product labeling, enclosures, and containers.[69] The manufacturing process is subject to significant scrutiny because changes or inconsistencies in the manufacturing process can cause changes to the biological product. In addition to data review, FDA performs an inspection of the manufacturing facility to ensure that the relevant establishments comply with the standards established in the BLA and the requirements prescribed in applicable regulations.[70]

Finally, under the Pediatric Research Equity Act (PREA),[71] BLAs for new active ingredients, new indications, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support administration of the product to pediatric patients.[72] Specifically, a pediatric assessment contains data from pediatric studies for various pediatric age groups to assess the safety and effectiveness of the proposed biological product for the claimed indications in relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the biological product has been assessed to be safe and effective.[73] Such studies are mandatory unless the requirement is waived, deferred, or inapplicable.[74]

B. Biosimilars and aBLAs

Statutorily created in 2010 under the BPCIA,[75] biosimilar applications are "abbreviated" BLAs in that they do not require submission of all of the elements of a BLA. This is because a biosimilar application, or an aBLA, relies on FDA's existing knowledge about the safety, purity, and potency

68. *Id*. § 601.2(a).

69. *Id*.

70. *Id*. § 601.20(c), (d).

71. Pub. L. No. 108-155, 117 Stat. 1936 (2003).

72. 21 U.S.C. § 355c(a)(1)(A)(ii).

73. FDA, Draft Guidance for Industry: Pediatric Drug Development: Regulatory Considerations—Complying with the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity under the Best Pharmaceuticals for Children Act 10–11 (2023), https://www.fda.gov/media/168201/download.

74. 21 U.S.C. § 355c(a)(4), (5).

75. Pub. L. No. 111-148, §§ 7001–7003.

of the reference product to support licensure.[76] An aBLA therefore must reference a biologic approved under a BLA pursuant to section 351(a) of the PHS Act—again, the "reference product"—and include information "to show that the [proposed product] is biosimilar to the reference product."[77] Biosimilarity means that the proposed 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 [proposed product] and the reference product in terms of the safety, purity, and potency of the product."[78] A biosimilar, however, is not substitutable for its reference product unless it is "interchangeable," which requires additional testing.[79]

Biosimilars are licensed under section 351(k) of the PHS Act, which requires the submission of an application including data demonstrating biosimilarity to the reference product to the FDA division that reviewed and approved the corresponding reference product.[80] While FDA has not defined the key terms "highly similar" or "clinically meaningful" in regulation, FDA has set forth various factors that it uses to determine whether products meet the statutory requirements.[81] Importantly, the showing needed to demonstrate biosimilarity to a reference product is significantly more rigorous than the bioequivalence standard used for generic drugs under the FDC Act. Rather than demonstrating mere equivalence in terms of bioavailability, equivalent safety and effectiveness must be demonstrated for approval of a biosimilar product.

Though the aBLA need not include "substantial evidence of effectiveness," it still must include clinical studies sufficient to demonstrate safety,

76. FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 3–4 (2015) [hereinafter Scientific Considerations in Demonstrating Biosimilarity Guidance], https://www.fda.gov/media/82647/download.

77. 42 U.S.C. § 262(k)(3).

78. *Id*. § 262(i)(2).

79. *Id*. § 262(i)(3).

80. *Id*. § 262(k)(2)(A); *id*. §262(k)(5)(B).

81. *See*, *e.g.*, FDA, Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (2015), https://www.fda.gov/media/135612/download; Scientific Considerations in Demonstrating Biosimilarity Guidance, *supra* note 76; FDA, Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (2016), https://www.fda.gov/media/88622/download; FDA, Draft Guidance for Industry: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (2019), https://www.fda.gov/media/159261/download; FDA, Draft Guidance for Industry: Biosimilars and Interchangeable Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed (2020) [hereinafter Biosimilars and Interchangeable Biosimilars Guidance], https://www.fda.gov/media/134932/download; FDA, Draft Guidance for Industry: Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act (rev. 1, 2023) [hereinafter Biosimilars Additional Q&A Guidance], https://www.fda.gov/media/172169/download.

purity, and potency in one or more conditions of use for which the reference product is licensed.[82] To that end, an aBLA must include data derived from analytical studies, toxicity assessments, clinical studies, or, where necessary, animal studies, all of which are at FDA's discretion.[83] These studies however are more limited in nature than a full BLA and may consist only of assessments of immunogenicity and pharmacokinetics or pharmacodynamics.[84] The aBLA must also include publicly available information regarding FDA's determination that the reference product relied on for approval is safe and effective[85] and may include "any additional information in support of the application, including publicly-available information with respect to the reference product or another biological product."[86]

It is important to note that the proposed biosimilar need not be exactly the same as its reference product, but it must be the same as its reference product in specific ways. The proposed product must "utilize the same mechanism or mechanisms of action" as the reference product.[87] The conditions of use in the labeling must have been approved for the reference product—though the biosimilars need not be approved for every use that its reference product is.[88] Additionally, the proposed product must have the same route of administration, dosage form, and strength as its reference product, and changes to any of those elements is not approvable as part of an aBLA; a new BLA or supplement to a BLA would be required to make any such changes.[89] And, after years of debate, FDA now requires biosimilars to have the same root name as their reference product with the addition of a distinctive suffix of four lower case letters to avoid confusion.[90]

Like the BLA, the aBLA must contain a Chemistry, Manufacturing, and Controls section, which demonstrates that the facility in which the

82. 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc).

83. *Id*. § 262(k)(2)(A)(i)(I); FDA, Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act 3 (rev. 2, 2021) [hereinafter Q&A on Biosimilar Development Guidance], https://www.fda.gov/media/119258/download.

84. 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc).

85. *See id*. §262(k)(2)(A)(iii)(I). FDA has commented that "publicly available information" includes, but is not limited to, the types of information found in the so-called "action package," *see* FDC Act §505(*l*)(2)(C), 21 U.S.C. §355(*l*)(2)(C), for a section 351(a) BLA. *See* Biosimilars Additional Q&A Guidance, *supra* note 81, at 11.

86. PHS Act §351(k)(2)(A)(iii)(II), 42 U.S.C. §262(k)(2)(A)(iii)(II).

87. 42 U.S.C. § 262(k)(2)(A)(i)(II).

88. Q&A on Biosimilar Development Guidance, *supra* note 83, at 21.

89. 42 U.S.C. § 262(k)(2)(A)(i)(IV); Q&A on Biosimilar Development Guidance, *supra* note 83, at 20.

90. *See* Designation of Official Names and Proper Names for Certain Biological Products, 80 Fed. Reg. 52,224 (proposed Aug. 28, 2015); FDA, Guidance for Industry: Nonproprietary Naming of Biological Products (2017), https://www.fda.gov/media/93218/download.

biosimilar is manufactured meets applicable standards to ensure safety, purity, and potency.[91] FDA will also perform a pre-licensure inspection.

Finally, biosimilars, like BLAs, are subject to PREA, assuming the aBLA is not interchangeable with the reference product. Under PREA, a biosimilar product (that is not interchangeable) is considered to have a "new active ingredient," which requires a pediatric assessment unless waived or deferred.[92] Such requirements apply only to the extent that compliance with PREA would not result in a condition of use that has not been previously approved for the reference product or a dosage form, strength, or route of administration that differs from the reference product.[93] Thus, when the reference product does not have pediatric use information in its labeling or an age-appropriate formulation for a relevant pediatric population, the biosimilar applicant would not be expected to obtain licensure for a pediatric use (or describe that use in product labeling).[94]

Additional requirements applicable to the conditions of use are also relevant for an aBLA. For example, if the reference product is subject to a Risk Evaluation and Mitigation Strategy, the aBLA will be as well.[95] And Congress currently is exploring whether there is a pathway for aBLAs to differ to some extent from their reference products through "bio-betters," which would allow for the development of new biologics based on FDA's findings for licensed biologics.[96]

Without all required elements of a BLA or an aBLA, FDA will "refuse to file" the license application, which means that FDA will not review the application until it has been resubmitted with all of the required information.[97] This slows down FDA's review process and may require payment of an additional user fee.[98]

C. Interchangeable Biosimilars

While biosimilar products only need to meet a "highly similar" standard, the threshold is higher for "interchangeable" biosimilars, which are biosimilars that "may be substituted for the reference product without the intervention of [a] health care provider."[99] Thus, applications for

91. 42 U.S.C. § 262(k)(2)(A)(i)(V).

92. Q&A ON BIOSIMILAR DEVELOPMENT GUIDANCE, *supra* note 83, at 12; 21 U.S.C. § 355c(a)(1)(A)(ii).

93. Q&A ON BIOSIMILAR DEVELOPMENT GUIDANCE, *supra* note 83, at 13.

94. *Id*. at 15.

95. *See* PHS Act §351(k)(5)(C), 42 U.S.C. §262(k)(5)(C).

96. This pathway would be similar to the 505(b)(2) regulatory pathway set forth in FDC Act § 505(b)(2), 21 U.S.C. § 355(b)(2).

97. CDER, FDA, MANUAL OF POLICIES AND PROCEDURES (MAPP), 6025.4 (2018).

98. *See infra* Section IV.

99. 42 U.S.C. § 262(i)(3).

interchangeable biosimilars require data to demonstrate that the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient."[100] Where the reference product is administered more than once to a patient, an applicant must provide sufficient information to show that the risks in terms of safety or efficacy of alternating and switching between the proposed product and the reference product are no greater than using the reference product without such a switch.[101]

Because an interchangeable biosimilar is a biosimilar, an aBLA or a supplement to an approved aBLA under PHS Act section 351(k) is required, but an interchangeable application contains additional data than the typical aBLA. Regardless of whether the interchangeable product is submitted in an aBLA or a supplement, the same evidence will be necessary for licensure. Such evidence might include:

- Identification and analysis of the critical quality attributes
- Identification of analytical differences between the reference product and the proposed interchangeable product with an analysis of the potential clinical impact of the differences
- Analysis of the mechanism of action in each condition of use for which the reference product is licensed, which may include analysis of the target receptor for each relevant activity/function of the product; binding, dose/concentration response, and pattern of molecular signaling upon engagement of target receptor or receptors; the relationship between product structure and target/receptor interactions; and the location and expression of target receptor or receptors
- Analysis of any differences in the expected pharmacokinetics and biodistribution of the product in different patient populations for which the reference product is licensed
- Analysis of any differences in the expected immunogenicity risk of the product in different patient populations for which the reference product is licensed
- Analysis of any differences in expected toxicities of the product in each condition of use and patient population
- Any other information that goes to the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed[102]

The data and information necessary to meet the interchangeability standard varies depending on the nature of the proposed interchangeable

100. *Id*. § 262(k)(4)(A).
101. *Id*. § 262(k)(4)(B).
102. *Id*.

product.[103] Not all factors will be relevant to every proposed interchangeable product. Product complexity and characterization capability and product-specific immunogenicity risk will dictate much of the information required to demonstrate interchangeability.[104] If applicable, the application should include scientific justification for any differences between the reference product and proposed interchangeable explaining that they can be expected to produce the same clinical result as the reference product in any given patient notwithstanding such differences.[105]

Switching studies, which assess the risks of alternating or switching between the reference product and the proposed product, are a critical element of the interchangeable biosimilar application for products that are intended to be administered more than once.[106] These studies should evaluate changes in treatment that result in two or more alternating exposures to the proposed interchangeable product and the reference product.[107] The design of such studies will depend on the product and its use in clinical practice, but they must assess whether switching results in differences in immunogenicity and pharmacokinetic and/or pharmacodynamics as compared to use only of the reference product.[108] FDA highly encourages sponsors to meet with the agency to discuss the planned development approach before commencing studies.[109]

Though an interchangeable aBLA may contain more data than a typical aBLA, interchangeable biosimilars are exempt from PREA requirements. This is because an interchangeable product is not considered to contain a new "active ingredient" for purposes of required pediatric testing.[110] However, if an applicant first seeks licensure of its proposed product as a biosimilar product (rather than an interchangeable biosimilar product), the applicant must address applicable PREA requirements in its non-interchangeable biosimilar product, even if the applicant ultimately intends to later seek licensure of the product as an interchangeable product.[111]

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103. FDA, Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product 4 (2019), https://www.fda.gov/media/124907/download.

104. *Id*. at 5–7.

105. *Id*.

106. *Id*. at 9.

107. *Id*.

108. *Id*. at 9–10.

109. *Id*. at 10.

110. *See* 21 U.S.C. §355c(*l*)(2). A non-interchangeable biosimilar product is considered to contain a new active ingredient, and, therefore, is subject to pediatric testing requirements. *See id*. §355c(*l*)(1).

111. Q&A on Biosimilar Development Guidance, *supra* note 83, at 12.

As of August 2023, only 42 biosimilars, four of which are interchangeable, have been approved in the United States.[112]

IV. User Fees

In order to seek approval of a BLA or an aBLA, the submission of a "user fee" is required. First implemented in 1992 to generate revenue in exchange for FDA's agreement to improve upon its historically slow review times, the Prescription Drug User Fee Act (PDUFA) requires NDA and BLA applicants to pay fees of a million dollars or more to simply to submit an application.[113] In turn, FDA has agreed to "performance goals," which are timeframes by which FDA agrees to review applications. Over time, Congress, with input from FDA, has adopted user fees for generic drugs, medical devices, and, after passage of the BPCIA, biosimilars. These user fees are reauthorized every five years under User Fee Acts, which, because they are "must-pass legislation," often are hosts for other bills that the agency wants Congress to pass. And each user fee bill seems to change its respective user fee program to some degree.

Under the current PDUFA, PDUFA VII, BLA sponsors must pay the agency an application fee for each application submitted, as well as program fees for ongoing support of approved applications. Application fees are assessed for each human drug application, including an original BLA, in amounts based on the types of data included in the application for approval. If the BLA contains clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness, the entire PDUFA fee of $4,048,695 for fiscal year (FY) 2024 must be paid before FDA will review the application; if the BLA contains none of the aforementioned clinical data, the user fee assessed is $2,024,348.[114] If FDA refuses to file the BLA, 75 percent of the application fee will be refunded.[115] And while there are some exemptions and some waivers and reductions available, most applications require this user fee. Failure to pay an application fee will preclude FDA from reviewing that application.

FDA also assesses a program fee annually for all prescription drug products identified in an approved BLA or NDA. Program fees for FY 2024

112. *See Biosimilar Product Information*, FDA, https://www.fda.gov/drugs/biosimilars/biosimilar-product-information (last updated Dec. 8, 2023).

113. Pub. L. No. -571, 106 Stat. 4491 (1992).

114. Prescription Drug User Fee Rates for Fiscal Year 2024, 88 Fed. Reg. 48,881, 48,882 (July 28, 2023).

115. *Prescription User Fee Amendments*, FDA, https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments (last updated Dec. 14, 2023).

are set at $416,429,[116] and sponsors must pay a separate program fee for each strength or potency of a drug product up to five strengths included in a single application (in addition to the application fee).[117] Again, there are some exemptions to the program fee, but most sponsors are required to pay. Failure to pay program fees deems an applicant "in arrears."[118] FDA maintains an "arrears list," and FDA will refuse to review any applications submitted by a sponsor on that list, even if the application fee has been paid for the given application.[119]

Biosimilars are subject to a similar, but much more recent, user fee scheme. The Biosimilar User Fee Act (BsUFA), enacted under the Food and Drug Administration Safety and Innovation Act, first established a biosimilar user fee in 2012.[120] Like PDUFA, it provides additional revenue so that FDA can hire staff, improve systems, and manage the biological review process smoothly.[121]

Under the current iteration of BsUFA, BsUFA III, Congress has imposed three types of user fees: biosimilar biological product development (BPD) fees, application fees, and program fees. The BPD fee is a one-time fee assessed to a sponsor who submits a meeting request to FDA for a BPD meeting or submits an IND intended to support a biosimilar biological product application. There is an initial BPD fee and annual BPD fee for each product under development. Like PDUFA fees, FDA assesses a user fee for each aBLA submission and an annual fee for each product that has been approved up to five program fees.[122] Both the initial BPD fee and annual BPD fee are $10,000 for FY 2024. The BsUFA application fee where clinical data is required is $1,018,753; where it is not, the fee is $509,377 for FY 2024. The program fee for FY 2024 is $177,397.[123]

Failure to pay BsUFA fees has similar consequences to PDUFA. If a sponsor fails to pay any BPD fee, FDA will refuse to provide a BPD meeting for the product for which fees are owed and may put a clinical investigation on hold.[124] If an application fee is not paid, FDA will refuse

116. 88 Fed. Reg. at 48,882.

117. *Id*. at 48,887.

118. CDER, FDA, Manual of Policies and Procedures (MAPP), 6050.1 (rev. 2, 2021).

119. *Id*. at 3.

120. Pub. L. No. 112-144, 126 Stat. 993 (2012).

121. *See* Reauthorization of the Biosimilar User Fee Act; Public Meeting; Request for Comments, 86 Fed. Reg. 52,685, 52,686 (Sept. 22, 2021).

122. *Biosimilar User Fee Amendments*, FDA, https://www.fda.gov/industry/fda-user-fee-programs/biosimilar-user-fee-amendments (last updated Oct. 3, 2023).

123. Biosimilar User Fee Rates for Fiscal Year 2024, 88 Fed. Reg. 48,855, 48,856 (July 28, 2023).

124. FDA, Guidance for Industry: Assessing User Fees under the Biosimilar User Fee Amendments of 2022 (2023), https://www.fda.gov/media/170634/download.

to review the application.[125] And failure to pay program fees gets an applicant on the arrears list.

V. Biologic and Biosimilar Approval Process

While FDA licenses a biological product under either a BLA or an aBLA, granting the application holder permission to introduce a biologic product into interstate commerce, the applicable requirements differ depending on the type of licensing application filed.[126] The timing for review also depends on the type of licensing application filed. But the process is the same: FDA reviews the application and either approves the application or comes back to the sponsor for additional information.[127]

Both BLAs and aBLAs must be "filed"—or accepted—by FDA to commence review. FDA will only file a BLA that includes sufficient information, on its face, to facilitate a complete review; in other words, it must contain all information required under the PHS Act.[128] FDA reviews the file for any deficiencies and will either refuse to file the BLA or aBLA or will accept the application and commence review. In certain cases, where the deficiencies appear to be correctable, FDA may work with the applicant to rectify these issues, but FDA has no obligation to do so.[129] FDA will notify an applicant within 60 days whether the application has been filed successfully.[130]

Once FDA has filed the application, the Review Division—assigned based on proposed therapeutic use—divides the application amongst different disciplines, such as clinical, pharmacology, product quality, biometrics, and manufacturing.[131] After submission and while the disciplines are reviewing the Review Division hosts the sponsors for various meetings, including filing/planning meetings, mid-cycle meetings, and wrap-up meetings, which may differ depending on whether the application is a BLA

125. CDER, FDA, Manual of Policies and Procedures (MAPP), 6050.2 (2021).

126. 21 C.F.R. § 601.2(a) (2024).

127. Theoretically, FDA could deny a license application, but this rarely happens.

128. FDA, Draft Guidance for Industry: Refuse to File: NDA and BLA Submissions to CDER 2 (2017) [hereinafter Guidance for Industry: Refuse to File: NDA and BLA Submissions], https://www.fda.gov/media/109758/download.

129. FDA, CDER 21st Century Review Process Desk Reference Guide: New Drug Application and Biologics License Application Reviews 20 [hereinafter CDER 21st Century Review Process Desk Reference Guide], https://www.fda.gov/media/78941/download.

130. Guidance for Industry: Refuse to File: NDA and BLA Submissions, *supra* note 128, at 2.

131. There are many more. *See* CDER 21st Century Review Process Desk Reference Guide, *supra* note 129, at 3.

or an aBLA.[132] Reviewers will also communicate with the applicant during the review cycle by asking for additional information through information requests or discipline review letters.[133] As part of the review, the reviewers may seek expert advice from other FDA divisions or centers, through an Advisory Committee meeting, or through other means.[134] Finally, FDA and the applicant engage in labeling and post-marketing requirement negotiations.[135]

FDA approval also requires an assessment of the manufacturing facilities for a given biological product. This is because manufacturing is key to the safety and efficacy of a biologic, and thus licenses for biologics will not be issued unless the manufacturing establishment complies with FDA regulations for the applicable current Good Manufacturing Practices.[136] FDA determines whether a pre-license or pre-approval inspection is necessary based on the risk profile of a given facility, and such inspections generally are necessary where FDA has not recently inspected the facility; the facility is new; there is a new production suite or significant manufacturing change within an existing facility; or the facility does not have a compliance history.[137]

FDA, as part of PDUFA and BsUFA, has committed to review schedule "goals" in which it will review an application. Under PDUFA, FDA has committed to reviewing 90 percent of original BLA submissions within ten months of the 60-day filing date—or within a year of submission—and to 90 percent of original BLA submissions that have been granted "priority review" within six months of the 60-day filing date—or within eight months.[138] Supplements to BLAs are expected to be reviewed within ten months for standard efficacy supplements and six months for priority efficacy supplements.[139] "Major amendments" to pending applications

132. *Id*. at 6.

133. *Id*. at 26.

134. *Id*. at 32.

135. *Id*. at 36–37.

136. CBER, FDA, SOP 8410: Determining When Pre-License/Pre-Approval Inspections Are Necessary 1–2 (2020).

137. *Id*. at 3.

138. FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027 [hereinafter PDUFA Commitment Letter FY 2023–2027], https://www.fda.gov/media/151712/download. "Priority review" is a designation awarded to a proposed product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness over available therapies. FDA, Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics 24 (2014), https://www.fda.gov/media/86377/download. Alternatively, priority review can be obtained through use of a priority review voucher, which is an incentive provided under the FDC Act for a variety of programs.

139. PDUFA Commitment Letter FY 2023–2027, *supra* note 138.

can extend the timeline by as many as three months.[140] For aBLAs, FDA commits to reviewing 90 percent of original aBLAs within ten months of the 60-day filing date (again, one year), and resubmitted aBLAs within six months of receipt (which does not include an additional 60-day filing date).[141] Like for BLAs, a "major amendment" may extend the review cycle.[142]

At the end of the review cycle—on or near the PDUFA or BsUFA goal date—FDA will either issue an approval letter or send an applicant a "complete response letter" (CRL), which lists all the deficiencies that are preventing the application from being approved.[143] Technically, FDA has the authority to deny a license, but, practically, the agency rarely does so.[144] Instead, FDA issues CRLs until the applicant either perfects or withdraws the application. Those CRLs state that an application cannot be approved in its current state and describe all of the deficiencies the agency has identified and provide agency recommendations of actions the applicant might take to facilitate approval.[145] In response, an applicant may resubmit the application, addressing all deficiencies identified in the CRL; withdraw the application; or take no action, which is treated as a withdrawal.[146] CRLs are incredibly common; many applications receive multiple before securing approval.

With small molecules, there would be patent considerations for both applications and abbreviated applications, but patents have no role in the regulatory approval process for biologics. Though patents are integral to the biologic development process and to the balance between innovation (usually considered the BLA) and access (typically the aBLA), patents on a given reference product do not block FDA from approving an aBLA. Patents may eventually be listed in FDA's "Purple Book"—its list of all biological products licensed under the PHS Act[147]—but that process is separate from the BLA and aBLA approval process.

140. *Id*.

141. FDA, Biosimilar Biological Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027, https://www.fda.gov/media/152279/download.

142. *Id*.

143. 21 C.F.R. § 601.3(a) (2024).

144. *See id*. § 601.4(b) ("If the Commissioner determines that the establishment or product does not meet the requirements established in this chapter, the biologics license application shall be denied. . . .").

145. *Id*. § 601.3(a).

146. *Id*. § 601.3(b), (c).

147. *See* Chapter 4.

VI. Available Exclusivities

As an incentive to innovate, Congress built in to the BPCIA regulatory exclusivities for eligible BLAs and interchangeable aBLAs.[148] Though built off the model set forth in the FDC Act, which provides exclusivity for new chemical entities, new clinical studies, and first-to-file generic drugs, the available exclusivities for biologics are very different than those for small molecules. For full BLAs, the BPCIA provides for 12 years of data exclusivity for a reference product—"reference product exclusivity"—precluding biosimilars from relying on that reference product for approval for 12 years. For interchangeable biosimilars, the BPCIA provides one year during which FDA cannot approve another interchangeable biosimilar. Notably, no exclusivity is available for biosimilars that are not interchangeable.

A. Reference Product Exclusivity

Under the BPCIA, reference products are protected by a 12-year period of reference product exclusivity. Under the statute, FDA cannot accept for review an aBLA—interchangeable or otherwise—relying on a given reference for four years after the date of "first licensure" or approve an aBLA relying on that reference product for 12 years.[149] Due to the way the statute is written, FDA explains exclusivity for a reference product in terms of "a prohibition on acceptance or approval of an application for a biosimilar or interchangeable product for a period of time starting from the date of first licensure."[150] Put another way, reference product exclusivity protects a new biological product from biosimilar competition for 12 years. Importantly, the reference product's exclusivity does not block approval of a BLA for the same molecule—meaning that any sponsor can file a BLA under section 351(a) of the PHS Act—but merely precludes approval of an application relying on that reference product's data for approval.[151]

Not all reference products are eligible for reference product exclusivity, however. Under the act, supplements to BLAs are not eligible for reference product exclusivity.[152] In practice, this means that new indications and new formulations do not qualify for reference product exclusivity even if completely new clinical trials were required for approval. Thus, each

148. 42 U.S.C. § 262(k)(6), (7).

149. *Id*. § 262(k)(7).

150. FDA, Draft Guidance for Industry: Reference Product Exclusivity for Biological Products Filed under Section 351(a) of the PHS Act 2 (2014) [hereinafter Guidance for Industry: Reference Product Exclusivity], https://www.fda.gov/media/89049/download.

151. *See* 42 U.S.C. § 262(k)(7)(A).

152. *Id*. § 262(k)(7)(C).

product is provided with a single period of reference product exclusivity, and, unlike with small molecules, there is no opportunity for a second period of exclusivity based on tweaks to the original formulation even if that tweak results in new, innovative features.

The statute further excludes from eligibility for reference product exclusivity "subsequent application[s] filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity)" for a change to the product, even if that change results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength.[153] The exception to the exclusion from reference product exclusivity eligibility is for a supplement from the same manufacturer that results in a "modification to the structure of the biological product that does not result in a change in safety, purity, or potency."[154] This means that unless a subsequent application for an approved biologic filed by the same sponsor has a different structure from the previously approved drug product, the new application is not eligible for exclusivity.

Notably, a subsequent BLA under section 351(a) of the PHS Act filed *by a different applicant for the same molecule* is also eligible for reference product exclusivity,[155] which makes the definition of the "same sponsor or manufacturer" important. While the "same sponsor or manufacturer" is clear—it means the same applicant as the approved BLA—FDA also interprets it to include a "licensor, predecessor in interest, or other related entity." These terms are subject to agency interpretation.

FDA examines the relationships between business entities involved in each BLA to determine eligibility of that BLA for reference product exclusivity.[156] FDA further elucidates in guidance how it will assess "licensor, predecessor in interest, or other related entity."[157] Specifically, FDA defines a "licensor" as any entity that has granted the sponsor a license to market the reference product, regardless of whether such license is exclusive.[158] A licensor includes a party that retains intellectual property rights over the biological product or otherwise has the right to develop, manufacture, or market the biological product.[159] FDA further defines a "predecessor in interest" as any entity that the sponsor has "taken over, merged

153. *Id*.

154. *Id*.

155. *See id*. (excluding from reference product exclusivity eligibility only subsequent applications filed by the "same sponsor or manufacturer" of a given product).

156. Guidance for Industry: Reference Product Exclusivity, *supra* note 150, at 4.

157. *See generally id*.

158. *Id*. at 5.

159. *Id*.

with, or purchased," has granted the sponsor exclusive rights to market the biologic under the BLA, or had exclusive rights to the data upon which the BLA was approved.[160] Thus, not only is FDA looking at the parties who currently own the intellectual property or other rights to market a product but also to any party that *previously* had such rights.

More complicated is the agency's examination of a "related entity." That ambiguous term is not defined anywhere in the PHS Act, so the agency has decided to look to control and ownership.[161] FDA will consider an entity a "related entity" to an applicant for purposes of reference product exclusivity where one party owns, controls, or has the power to own or control the other, either directly or through other entities.[162] If the parties are under common ownership or control, they are also considered "related entities."[163] Alternatively, the agency may consider two parties related entities if they were engaged in commercial collaboration to develop the product at issue, excluding "service contracts" like contract research organizations.[164] However, it is not clear exactly what FDA is looking for and the extent of collaboration necessary to meet the threshold for a "related entity": FDA assesses this on a case-by-case basis.

A subsequent application *could* be eligible for another period of reference product exclusivity but only where there is a "modification to the structure of the biological product" and that modification results in a "change in safety, purity, or potency."[165] FDA therefore reviews each product submitted in a subsequent application to determine whether it constitutes a modification to the structure of a previously licensed product.[166] As part of that review, FDA examines, based on both materials provided by the sponsor and its own scientific analysis, the structural similarities and differences between its proposed product and any previously licensed biological product that was the subject of a section 351(a) application filed by the same sponsor or manufacturer (or its licensor, predecessor in interest, or other related entity).[167] For protein products, structural differences assessed include, as appropriate, any differences in amino acid sequence, glycosylation patterns, tertiary structures, post-translational events (including any chemical modifications of the molecular structure such as pegylation), and infidelity of translation or transcription, among others.[168]

160. *Id*.
161. *Id*.
162. *Id*.
163. *Id*.
164. *Id*.
165. 42 U.S.C. § 262(k)(7)(C)(ii).
166. Guidance for Industry: Reference Product Exclusivity, *supra* note 150, at 5–6.
167. *Id*. at 5.
168. *Id*. at 5–6.

FDA also will consider the principal structural molecular features of two related products, as well as the molecular target.[169] Importantly, modification of a structure will not be presumed; it requires a sponsor to submit to the BLA an explanation of the change.[170] Each assessment of such a modification is made on a case-by-case basis.[171]

Once FDA determines there is a modification to the structure of a biologic, it then looks to see whether that structural modification has resulted in a change in safety, purity, or potency such that the proposed product has a different safety or efficacy profile than the previously licensed product.[172] That determination is also made on a case-by-case basis as supported by data submitted to the BLA by the sponsor.[173] FDA will look at measurable effects (typically demonstrated in preclinical or clinical studies) describing how the *modification resulted in a change* in safety, purity, or potency compared to the previously licensed product.[174] FDA will presume a change to the proposed product's safety, purity, or potency if the proposed product affects a different molecular target—a molecule whose activity is modified by the product—than the original product, as long as it results in a *desirable* therapeutic effect.[175] Such molecular targets can include receptors, enzymes, ion channels, structural or membrane transport proteins, nucleic acids, and pathogens, among others.[176] That the change will provide a meaningful benefit to public health is also supportive of such a change.[177] If FDA determines that there is such a modification, the modified product will be eligible for its own period of reference product exclusivity.[178]

An applicant should include a request for reference product exclusivity in its BLA. That request should include a list of all licensed biological products structurally related to the reference product, including products that share some of the same principal molecular structural features and products that affect the same molecular target.[179] If any of those products were sponsored by affiliates, licensors, predecessors in interest, or related entities of the applicant, such parties should be identified in the request. FDA also expects to see a description of the structural differences between the proposed product and any structurally similar products identified in

169. *Id*. at 6.
170. *Id*. at 5–6.
171. *Id*.
172. *Id*. at 6–7.
173. *Id*. at 6.
174. *Id*.
175. *Id*.
176. *Id*.
177. *Id*.
178. *Id*. at 7.
179. *Id*. at 7–8.

the list. Finally, FDA requests any information supporting a change in the safety, purity, or potency of the proposed product, including a description of how structural differences relate to such changes.[180]

Once FDA has reviewed a request for exclusivity and made a final determination about whether a given product is eligible for reference product exclusivity, FDA notifies sponsors by publication in the Purple Book. To do so, FDA assigns a date of "first licensure" in the Purple Book, which serves as the start of the 12-year exclusivity period. The listing of such date signifies that the product qualifies for reference product exclusivity and the date on which the exclusivity will expire.[181] In most instances, the date of first licensure will be the initial date the BLA for a particular product at issue was first licensed in the United States.[182]

B. Biosimilar Exclusivity

While the BPCIA created a pathway for biosimilars under section 351(k), it did not provide exclusivity for biosimilar application absent a determination that a particular biosimilar is interchangeable with its reference product.[183] Thus, biosimilar exclusivity does not exist; however, exclusivity for the first *interchangeable* biosimilar for such a reference product is available, reflecting Congress's intent to encourage development of biosimilars that could be substituted for the reference product without intervention of a health care professional.

"Interchangeable exclusivity" is awarded to the first applicant that obtains FDA approval of its product as an interchangeable product.[184] That exclusivity prevents FDA from approving another interchangeable application for the same reference product until the earlier of:

- One year after commercial marketing of the interchangeable biosimilar protected by exclusivity
- 18 months after a final court decision—defined as a decision of a court from which no appeal (other than to the U.S. Supreme Court) has been or can be taken—on or dismissal of any and all patent infringement litigation brought by the reference product sponsor against the interchangeable product sponsor
- 42 months after approval of the first interchangeable product if the patent infringement action brought against the first interchangeable product applicant is still ongoing

180. *Id*. at 8.
181. *Id*. at 1.
182. *Id*. at 3.
183. *See* 42 U.S.C. § 262(k)(6) (providing exclusivity only for interchangeable biosimilars).
184. *Id*.

- 18 months after approval of the first interchangeable product if the applicant has not been sued by the reference product sponsor[185]

The "first interchangeable biosimilar biological product" is defined as any interchangeable biosimilar biological product that is approved on the first day on which such a product is approved as interchangeable with the reference product.[186] Under the statute, therefore, the first interchangeable biosimilar referencing a given reference product is eligible for one year of exclusivity, but that exclusivity can be forfeited if the product is not marketed within 18 months or 42 months, depending on the status of patent litigation under the "patent dance" established under the BPCIA.[187]

Like reference product exclusivity, interchangeable exclusivity is marked in the Purple Book.[188] A date or the term "Date TBD" indicates that FDA has determined that the interchangeable product is eligible for interchangeable exclusivity, but FDA has not yet determined the period of exclusivity or if that exclusivity has been forfeited. The absence of a date, however, cannot be interpreted to mean that FDA has decided that a given interchangeable *is not eligible* for interchangeable exclusivity; FDA may not have made that determination yet.[189] And indeed, FDA is often slow to make such a determination.

C. Other Exclusivities

In addition to the BPCIA-enacted exclusivities, BLAs are eligible for orphan drug exclusivity and pediatric exclusivity. Technically, these exclusivities arise under the FDC Act rather than the PHS Act, but they apply to biological products as well. These exclusivities, as they are intended to reward development of new drugs in specific patient populations, are available only to full BLAs rather than biosimilars or interchangeable biosimilars.

To incentivize the development of drug products, including biological products, to treat rare medical conditions, the Orphan Drug Act provides, among other benefits like tax breaks and development assistance, seven years of exclusivity for a reference product indicated for a rare disease or condition during which FDA cannot approve a biosimilar or

185. *Id*.
186. *Id*.
187. *Id*.; *see* Chapter 4.
188. *Purple Book Database of Licensed Biological Products FAQs*, FDA, https://purplebooksearch.fda.gov/faqs (last visited Feb. 6, 2024) (Q3: What does the first interchangeable exclusivity date indicate?).
189. *Id*.

interchangeable biosimilar that references this product.[190] To qualify for this exclusivity, the agency must designate the drug product proposed as a drug to treat a rare disease or condition prior to the submission of an NDA or BLA.[191] To be designated a treatment for a "rare disease or condition," FDA must find either that the disease or condition that the BLA product's therapeutically active component is intended to treat "affects less than 200,000 persons in the United States" or that the targeted disease or condition affects more than 200,000 people and "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" (the "cost-recovery clause").[192] While FDA "shall designate the drug as a drug for such disease or condition" in either of those situations, FDA has rarely—and not recently—designated products by way of the cost-recovery clause.[193]

Once a drug with orphan drug designation is approved, FDA awards the application orphan drug exclusivity.[194] Orphan drug exclusivity prohibits FDA from approving for seven years "the same drug for the same disease or condition" for which the orphan-protected drug product is approved.[195] In assessing "same drug," FDA looks at the therapeutically active component, which, for large molecules like biological products, is the product's "principal molecular structural features," in order to ensure that small differences in macromolecules do not circumvent exclusivity.[196] FDA regulations establish sameness standards specifically for protein drugs, polysaccharide drugs, polynucleotide drugs, and "closely related, complex partly definable drugs with similar therapeutic intent."[197] Sameness, however, can be overcome by a showing that a drug is "clinically superior" to the previously approved drug by way of greater safety, greater

190. Pub. L. No. 97-414, § 1(b), 96 Stat. 2049, 2049 (1983); *see also* H.R. REP. NO. 97-840, at 1 (1982); 21 U.S.C. § 360cc(a).

191. 21 U.S.C. § 360bb(a)(1) ("A request for designation of a drug shall be made before the submission of an [NDA or BLA] for the drug.").

192. *Id*. § 360bb(a)(2).

193. *Id*. § 360bb(a)(1).

194. *Id*. § 360cc(a).

195. *Id*.

196. 21 C.F.R. § 316.3(b)(14)(ii) (2024); *see also* Orphan Drug Regulations, 56 Fed. Reg. 3,338, 3,341 (proposed Jan. 29, 1991) (explaining that FDA focuses on the designated large molecule's principal structural features because "it is possible to make changes in macromolecules that are very likely to have no pharmacologic effect (e.g., a substitution of one amino acid for another similar one at an unimportant site in the molecule), but that could nonetheless defeat exclusive marketing if any structural difference were sufficient to make drugs different for purposes of orphan-drug exclusive marketing" and noting that "small differences may affect the function of macromolecules much less than that of small molecules").

197. 21 C.F.R. § 316.3(b)(14) (2024).

effectiveness, or a major contribution to patient care.[198] A product may have both orphan drug exclusivity and reference product exclusivity, but the exclusivities run concurrently.[199]

Importantly, Orphan drug exclusivity—unlike reference product exclusivity—can be "carved out" or omitted from labeling of a biosimilar or interchangeable biosimilar relying on an exclusivity-protected orphan reference product.[200] This is because orphan drug exclusivity is condition-specific—it blocks applications for the same molecule for the same disease or condition—meaning that an application referencing a reference product that has a non-orphan-protected indication can still be approved but not for the protected indication.[201] When that exclusivity expires, the biosimilar or interchangeable applicant may submit a supplement to add the orphan indication to its labeling.

VII. Pediatric Exclusivity

Reference products are also eligible for a six-month extension of reference product exclusivity or orphan drug exclusivity as a reward for performing certain clinical studies on pediatric patient populations.[202] To be eligible for such exclusivity, FDA must issue a written request for pediatric studies, the study must be completed, and FDA must determine that the product meets the requirements set forth in the written request.[203] Pediatric exclusivity only extends existing exclusivities; thus, if a given product has no reference product exclusivity or orphan drug exclusivity, no pediatric exclusivity can be awarded.[204]

198. *Id*. § 316.3(b)(14)(ii); *id*. § 316.3(b)(3).

199. Guidance for Industry: Reference Product Exclusivity, *supra* note 150, at 2–3.

200. Biosimilars and Interchangeable Biosimilars Guidance, *supra* note 81, at 3.

201. *See id*. at 3–4 ("FDA may be able to license a biosimilar or interchangeable product for one or more indications of the reference product that are not protected by orphan-drug exclusivity.").

202. 42 U.S.C. § 262(m).

203. *Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)*, FDA, https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently (last updated Mar. 1, 2022).

204. *See* 42 U.S.C. § 262(m) (limiting pediatric exclusivity to extension of existing exclusivities). This differs from the FDC Act, which adds the six months of pediatric exclusivity both to patents and to exclusivities. This is because patents play a more limited role in the approval process for biological products.

VIII. Patent Considerations

While patents play a much more limited role in the approval process for biosimilars and interchangeable biosimilars than in small-molecule generic drug approval, they remain relevant. There is no patent listing or certification process, meaning that the patents for a given reference product do not serve as a regulatory block to approval; FDA can approve an aBLA at any time regardless of whether there is existing patent protection for a given reference product. In other words, FDA leaves the patents to the parties and the courts to sort out, as explained in Chapter 4. Other than affecting eligibility for interchangeable exclusivity, related patent litigation does not delay FDA approval.

BLAs are eligible for patent term extensions, which increase a patent's life, to make up for the time lost during which the product was in development or under FDA review. A patent term extension extends the patent term by half of the time the product spent in the testing process and all of the time the product was in review, up to five years.[205] The patent term extension cannot extend the remaining term of a patent beyond 14 years of the date of approval.[206] Only one patent per BLA can be extended.[207]

Even though patents are not part of the FDA approval or licensure process, patents covering a biological product do need to be listed in the Purple Book when the patent has been asserted by the applicant as part of the exchange of patent lists described in Chapter 4.[208] The Purple Book thus contains a list of patents and their expiration dates.[209] FDA's role in maintaining that patent list, however, is ministerial, and the patents listed do not affect timing of FDA approval or licensure of a given biosimilar or interchangeable biosimilar.

IX. Conclusion

Biological products and biosimilars are complex and licensure of both takes a significant investment in scientific data, which costs both time and money. Biological products are rewarded for that investment with a 12-year period of reference product exclusivity, and interchangeable biosimilars with one year of interchangeable exclusivity. This system is intended to benefit patients by encouraging access to both innovative new

205. 35 U.S.C. § 156.
206. *Id*.
207. *Id*.
208. *See* Chapter 4 (explaining the exchange of patent lists).
209. 42 U.S.C. § 262(k)(9)(A)(iii).

medicines and affordable substitutable versions of older ones. And biosimilar applications, which may not be eligible for exclusivity, can take advantage of an abbreviated pathway to market. The BPCIA and the biosimilar pathway thus has something for everyone.

FDA approval or licensure, however, is not the end of the story. Access to, and launch of, biosimilars and interchangeable biosimilars is also dependent on the outcome of the complicated "patent dance," as discussed in the next chapter.