Dear Sir or Madam:

On behalf of Boehringer Ingelheim Pharmaceuticals, Inc. (“Boehringer Ingelheim”), the undersigned hereby submits this Citizen Petition pursuant to 21 C.F.R. §§ 10.25 and 10.30 and section 351 of the Public Health Service Act (“PHS Act”), 42 U.S.C. § 262, to request the Commissioner of Food and Drugs to interpret the term “strength” in section 351(k) of the PHS Act for parenteral solutions to mean “total drug content,” without regard to concentration. Such action is necessary to: (1) ensure the Food and Drug Administration’s (“FDA’s” or “the Agency’s”) interpretation is consistent with the clear meaning of the Biologics Price Competition and Innovation Act (“BPCIA”); (2) prevent abusive “evergreening” tactics from stifling competition of affordable biosimilar and interchangeable biological products; and (3) maintain fair and consistent treatment of all similarly situated parenteral biological products.

Boehringer Ingelheim submits that FDA’s current interpretation of “strength” conflicts with the express terms and purpose of the BPCIA. Specifically, FDA has adopted a final policy that the “strength” of an injectable biological product (i.e., parenteral solution) is based on both the total content of drug substance (in mass or units of activity) and the concentration of drug substance (in mass or units of activity per unit volume). FDA thus takes the position that the “same strength” requirement in section 351(k) of the PHS Act requires a biological product approved under the 351(k) pathway to have the same concentration of drug substance as the reference product (“RP”), not just the same total drug content.

For the reasons discussed below, this interpretation of “strength” is incorrect as a matter of both law and policy. First, it conflicts with the clear meaning of “strength” – an unambiguous term of art – which Congress

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adopted when it passed the BPCIA in 2009. Second, FDA’s interpretation is unreasonable because it encourages, or at least permits, brand sponsors to use minor concentration changes as an anti-competitive tactic to prevent competition from biosimilar and interchangeable biological products, thereby depriving patients from accessing more affordable biological products, contrary to the goals of the BPCIA. Third, it is arbitrary and capricious because it treats parenteral solutions differently than other similarly situated parenteral products, such as lyophilized powders, without adequate justification. Finally, even assuming Boehringer Ingelheim’s other arguments do not compel an interpretation of “strength” to mean only “total drug content,” FDA should still exercise discretion to change its policy because that definition better promotes the goals of the BPCIA, and there are no countervailing regulatory interests that outweigh this important benefit. Accordingly, FDA should reverse this policy and interpret “strength” to mean “total drug content” without regard to concentration.

I. Actions Requested

For the reasons set forth below, Boehringer Ingelheim respectfully requests the Commissioner to take the following actions with respect to parenteral solutions regulated as biological products under section 351 of the PHS Act (42 U.S.C. § 262):

1. Interpret the term “strength” as used in section 351(k) of the PHS Act (42 U.S.C. § 262(k)) to mean the “total drug content” in the relevant container (e.g., single-dose vial, prefilled syringe) without regard to concentration or total volume;

2. Revise applicable Agency guidance documents, including FDA’s Draft Guidance for Industry: New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (Dec. 2018), Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1) (Dec. 2018), and Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act (Nov. 2020), to be consistent with this interpretation; and

3. Apply this interpretation to pending and approved 351(k) applications, amendments, and supplements, including in advice provided during Biosimilar Biological Product Development (“BPD”) meetings and in review correspondence (e.g., Complete Response Letters).

The grounds for these requests are set forth in detail below.
II. Statement of Grounds

A. FDA’s Final Interpretation of “Strength” and Its Harm to the Regulated Industry

1. The Biologics Price Competition and Innovation Act (BPCIA)

The BPCIA was passed by Congress in 2009 and signed by the President in 2010 to create an abbreviated pathway for the licensure of biosimilar and interchangeable biological products subject to regulation under the PHS Act. Pub. L. No. 111-148, Title VII, Subtitle A (2010). Modeled after the Hatch-Waxman Act’s abbreviated approval pathway for generic drugs, the BPCIA was intended to serve the same dual goals of “balancing innovation and consumer interests.” Pub. L. No. 111-148, § 7001(b).

Under the PHS Act, as amended by the BPCIA, FDA is authorized to approve a “biosimilar” if: (1) the biological product is “highly similar” to a single RP notwithstanding minor differences in clinically inactive components; and (2) there are no clinically meaningful differences between the two products in terms of safety, purity and potency. 42 U.S.C. § 262(i)(2). Biosimilarity must be demonstrated by means of robust analytical studies and non-clinical and clinical testing, including an assessment of immunogenicity (unless waived). Id. § 262(k)(2)(A)(i)(I).

The BPCIA also authorizes FDA to approve “interchangeable” biological products. A biological product will be considered “interchangeable” if it “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.” Id. § 262(i)(3). To be approved as “interchangeable,” a biological product not only must be biosimilar to the RP but also must be “expected to produce the same clinical results as the [RP] in any given patient.” Id. § 262(k)(4)(A). In addition, for biological products that are administered more than once, the risks associated with alternating or switching between products in terms of safety or diminished effectiveness must be no greater than the risk of using the RP without such alternating or switching. Id. § 262(k)(4)(B).

The BPCIA also imposes several general requirements for licensure under the 351(k) pathway. Specifically, the proposed biological product must:

- utilize the same mechanism of action as the RP (to the extent known);
- have labeling that prescribes, recommends, or suggests only conditions of use that were previously approved for the RP;
- use the same route of administration and dosage form as the RP; and
- be manufactured, processed, packed, or held in a facility that meets current Good Manufacturing Practice (“cGMP”) standards.

Id. §§ 262(k)(2)(A)(i)(II), (III), (IV), (V).

Finally, and particularly relevant here, FDA cannot approve a biological product under the 351(k) pathway unless – like a proposed generic drug seeking approval under the Hatch-Waxman
Act’s Abbreviated New Drug Application (“ANDA”) pathway – it has the same “strength” as the RP. \textit{Id}. § 262(k)(2)(A)(i)(IV).

2. FDA’s Final Interpretation of “Strength” in the BPCIA

When the BPCIA was enacted in 2010, most biological products were licensed as parenteral solutions. That remains true today. Beginning as early as 2012, FDA adopted a policy that the “strength” of such products encompasses both total drug content and concentration. FDA first announced this interpretation of the term “strength” in a 2012 draft guidance document, which stated:

In general, we expect injectable biological products to have both the same total content of drug substance (in mass or units of activity in a container closure) and the same concentration of drug substance (in mass or units of activity per unit volume) as the reference product to have the same “strength” under section 351(k)(2)(A)(i)(IV) of the PHS Act.


Three years later, in an April 2015 guidance document, FDA finalized this interpretation of “strength” without revision. FDA, \textit{Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009}, p. 12 (April 2015) (“2015 Final Guidance”) (Exhibit 2). Under this interpretation, for a proposed biological product to meet the BPCIA’s “strength” requirement, it must have the same total drug content \textit{and} the same concentration of drug substance as the RP. This means that a proposed product with a different concentration than the RP cannot be licensed via the 351(k) pathway as either biosimilar or interchangeable because FDA considers it to have a different “strength” than the RP – even if it contains the exact same amount of drug substance per container and per dose.

In 2018, FDA moved its interpretation of “strength” from the 2015 Final Guidance back to a draft guidance document. FDA, \textit{New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)}, pp. 5-6 (Dec. 2018) (“2018 Draft Q&A Guidance”) (Exhibit 3). But the operative language remains the same: it continues to require consideration of both total drug content \textit{and} concentration. Specifically, the 2018 Draft Q&A Guidance states:

In general, a sponsor of a proposed biosimilar product or proposed interchangeable product with an “injection” dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) \textit{and the same concentration of drug substance} (in mass or units of activity per unit volume).
This Agency position has been expressed consistently throughout the various iterations of the guidance documents (both draft and final) since at least 2012. Although the current guidance is styled as a “draft,” there is no indication that FDA’s interpretation of “strength” as applied to “injection” dosage forms (i.e., parenteral solutions) is under active consideration. On the contrary, it appears FDA moved the discussion of “strength” from final to draft form in 2018 solely because of proposed changes to how strength is determined for dry solids from which a constituted or reconstituted solution is prepared (e.g., lyophilized powders), not because FDA is reconsidering how strength is determined for parenteral solutions.

The regulatory history of the guidance documents supports this conclusion. In both the 2012 Draft Guidance and the 2015 Final Guidance, FDA treated parenteral solutions and dry solids intended for injection in exactly the same way with regard to “strength” determinations, requiring consideration of both total drug content and concentration for both categories of parenteral biologics. In the 2018 Draft Q&A Guidance, however, FDA now is proposing to treat dry solids intended for reconstitution and injection differently than parenteral solutions by defining the strength of dry solids (but not parenteral solutions) to mean “total drug content” without regard to concentration. See 2018 Draft Q&A Guidance, p. 5 (for a dry solid, “a sponsor can demonstrate that the product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity).”). FDA explains that, for dry solids, the concentration of the product after reconstitution is “not a part of demonstrating same ‘strength[.]’” See 2018 Draft Q&A Guidance, p. 5. For parenteral solutions, by contrast, FDA continues to treat concentration as an integral part of strength.

Accordingly, FDA has adopted a final policy regarding the meaning of “strength” for parenteral solutions that requires consideration of both total drug content and concentration. Although this policy currently is set forth in draft guidance, it nevertheless represents FDA’s current and final interpretation of the BPCIA.

3. **Adalimumab Biological Products**

Humira® (adalimumab) was approved in 2002 via a 351(a) Biologics License Application (“BLA”). It originally was approved in a single, 40 mg strength (total drug content) with a 50 mg/mL concentration (40 mg/0.8 mL), but FDA approved additional strengths and concentrations over the following years. Humira currently is available in four different strengths: 10 mg, 20 mg, 40 mg, and 80 mg per container. It is approved and marketed in both (1) its original concentration (“OC”) formulation of 50 mg/mL for the three lower strengths (approved December 31, 2002 and marketed since January 2003); and (2) a higher concentration (“HC”) formulation of 100 mg/mL for all strengths (first approved in November 2015 and marketed in July 2018). The Humira OC formulation contains citrate whereas the HC formulation is citrate-free.

Boehringer Ingelheim is the marketing authorization holder of Cyltezo® (adalimumab-adbm), a biological product that was licensed on August 25, 2017 via a 351(k) BLA (BLA 761058) as a biosimilar to Humira. Cyltezo is approved in two strengths – 20 mg and 40 mg – in a 50 mg/mL concentration formulation that is citrate-free. Five other biosimilar adalimumab
products have been licensed by FDA via the 351(k) pathway, each of which is approved only as a 50 mg/mL concentration formulation.

In Boehringer Ingelheim’s view, these biosimilar products, including Cyltezo, should be considered to have the same “strength” as the corresponding OC and HC versions of Humira because they contain the same total drug content per container (e.g., 40 mg), regardless of the volume of excipients. This interpretation of “strength” would give sponsors of adalimumab products with OC formulations, like Cyltezo, the opportunity to submit a section 351(k) application seeking biosimilarity and/or interchangeability determinations that apply to Humira’s HC formulation.

Under FDA’s current interpretation of “strength,” however, no currently approved OC adalimumab product can be considered biosimilar or interchangeable to Humira’s HC formulation because the products have different concentrations. According to FDA’s final policy, two products with different concentrations will always be considered to have different “strengths” – even if (like here) they contain the same total drug content per container and per dose. On information and belief, FDA has been applying this interpretation of the term “strength” routinely and consistently to biological products seeking approval via 351(k) applications since at least 2015 when it issued the 2015 Final Guidance (and possibly earlier).

FDA’s final interpretation of “strength” has a direct and immediate impact on members of the regulated industry. FDA’s interpretation prevents a biological product with the same total drug content but a different concentration than the RP from being licensed as a biosimilar or interchangeable biological product, thereby impairing price competition and access to affordable biological products. Biosimilar manufacturers and/or sponsors, including Boehringer Ingelheim, are currently left with no option but to invest in the expensive and time-consuming process of developing biosimilar products with identical concentrations to the relevant RP even if they can prove that the proposed product is highly similar to and produces the same clinical results in terms of safety, purity, and potency as all concentrations of the RP. That hurts manufacturers, sponsors, and patients, and is contrary to the intent of the BPCIA.

B. FDA’s Interpretation of “Strength” Conflicts With the BPCIA, Is Unreasonable, and Is Arbitrary and Capricious

For the reasons discussed below, FDA’s interpretation of “strength” (1) conflicts with the clear language of the BPCIA, (2) unnecessarily and unreasonably facilitates the type of anti-competitive “game-playing” Congress sought to prohibit when it enacted the BPCIA, and (3) is arbitrary and capricious because it treats injectable solutions (like Cyltezo) differently than similar situated parenteral products (e.g., lyophilized powders), without any reasonable basis. To comply with the clear mandate of the BPCIA, FDA must interpret the “strength” of parenteral solutions to mean “total drug content” without regard to concentration.

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1 See Wash. Legal Found. v. Kessler, 880 F. Supp. 26, 35 (D.D.C. 1995), vacated on other grounds, Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000) (“Once the agency publicly articulates an unequivocal position … and expects regulated entities to alter their primary conduct to conform to that position, the agency has voluntarily relinquished the benefit of postponed judicial review.” (internal quotes and citations omitted)).
1. Legal Standard

An individual or entity that suffers a legal wrong or that is adversely affected by an agency action may seek judicial review of that action. 5 U.S.C. § 702. The reviewing court may set aside agency actions that are, among other things, “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law” or “in excess of statutory jurisdiction, authority, or limitations, or short of statutory right.” 5 U.S.C. § 706.

Because FDA’s interpretation of the BPCIA may be subject to judicial review, FDA’s interpretation of the BPCIA definition of “strength” must be analyzed under the well-known, two-step *Chevron* test established by the U.S. Supreme Court in 1984. Under the first step, a reviewing court must determine “whether Congress has directly spoken to the precise question at issue.” If the statutory language is plain and unambiguous and “the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.”

In making this determination, courts apply traditional tools of statutory construction to determine Congressional intent, including an examination of the statute’s text, structure, and purpose, as well as use of established canons of statutory construction. Typically, the statutory language itself and the structure and purpose of the statute as a whole are the most powerful indicators of Congressional intent. In addition, courts are careful not to interpret a statutory provision in isolation but instead strive to consider the context in which it is used, taking into account the entire statutory scheme and the overriding goals of the legislation.

If a court concludes that the statute is either silent or ambiguous on the precise question at issue, the second *Chevron* step is to determine whether the interpretation proffered by the agency is “based on a permissible construction of the statute.” “[A]mbiguity is not a license for the FDA

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4 *Chevron*, 467 U.S. at 842-43; *see also* *Carcieri v. Salazar*, 555 U.S. 379, 387 (2009).


7 *Robinson v. Shell Oil Co.*, 519 U.S. 337 (1997); *Stat-Trade*, 869 F. Supp. 2d at 102; *Serono Labs.*, 158 F.3d at 1319.

8 *Chevron*, 467 U.S. at 843.
to adopt any interpretation it chooses.”9 Rather, FDA’s interpretation survives *Chevron* step two only if the Agency provides “a reasonable explanation for how its interpretation serves the statute.”10 “This analysis overlaps substantially with the APA’s ‘arbitrary and capricious’ inquiry because ‘[w]hether a statute is unreasonably interpreted is close analytically to the issue whether an agency’s actions under a statute are unreasonable.’”11 Significantly, “[t]his is a requirement an agency can fail.”12

Finally, the Administrative Procedure Act (“APA”) precludes agency action that is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706(2)(A). Under this standard, an agency’s decision must be the product of “reasoned decision making.”13 An agency action normally will be set aside as “arbitrary and capricious” if the agency “has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.”14

Moreover, to satisfy the arbitrary and capricious standard, an agency “must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.”15 “Government is at its most arbitrary when it treats similarly situated people differently.”16 Consequently, “[i]f an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the APA.”17

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10 *Id.*

11 *Amarin*, 106 F. Supp. 3d 196, 217; see also *Agape Church, Inc. v. FCC*, 738 F.3d 397, 410 (D.C. Cir. 2013) (“The analysis . . . under *Chevron* Step Two and arbitrary and capricious review is often the same, because under *Chevron* step two, [the courts asks] whether an agency interpretation is arbitrary or capricious in substance.” (internal quotes omitted)).

12 *Braeburn*, 389 F. Supp. 3d at 20 (citing *Kisor*, 139 S.Ct. 2400, 2416).


14 *Id.* at 43.


2. **FDA’s Interpretation of Strength Conflicts with the Clear Language of the BPCIA (Chevron Step One)**

FDA’s interpretation of “strength” conflicts with the clear language of the BPCIA because it ignores the well-established meaning of that term in the years leading up to and through enactment of the BPCIA (2003 through 2010) – the relevant period for interpreting Congress’s intent. In the Hatch-Waxman Act, “strength” was a term of art used to mean, for parenteral solutions, **total drug content**. When Congress passed the BPCIA in 2009, it borrowed the terms “strength” and “same strength” directly from the Hatch-Waxman Act, thereby incorporating their existing, well-established administrative meanings. Accordingly, under *Chevron* step one, the meaning of “strength” in the BPCIA is clear and unambiguous—it means “total drug content,” without regard to concentration. Because FDA’s modified interpretation of “strength” (incorporating “concentration”) is inconsistent with this clear meaning, it conflicts with the BPCIA.

a. **“Strength” Is a Term of Art Incorporated Into the BPCIA That Means “Total Drug Content”**

Prior to the BPCIA, the PHS Act provisions governing the licensure of biological products did not include an abbreviated approval pathway, nor did they include any textual references to “strength.” 42 U.S.C. § 262 (2006). When fashioning the BPCIA’s new streamlined approval pathways for biosimilar and interchangeable biological products, Congress borrowed heavily from the Hatch-Waxman Act’s process for approving generic drugs.18 Of relevance here, Congress imported the Hatch-Waxman Act’s “strength” requirement directly into the BPCIA. The Hatch-Waxman Act generally requires that a generic drug have the “same strength” as its RP, *i.e.*, the single listed drug upon which it relies for approval. See 21 U.S.C. § 355(j)(2)(A)(iii). Likewise, the BPCIA requires that biosimilar and interchangeable biological products have the same “strength” as the RP. 42 U.S.C. § 262(k)(2)(A)(i)(IV). Consequently, although there are several obvious differences between the BPCIA and the Hatch-Waxman Act (*e.g.*, patent linkage),19 the “same strength” requirement is not one of them. On the contrary, it was transplanted root and branch directly from the Hatch-Waxman Act.

This is significant because when Congress passed the BPCIA in 2009 (and when the BPCIA was enacted in 2010), “strength” was a term of art that had a clear, unambiguous, and longstanding meaning for purposes of the Hatch-Waxman Act as applied to parenteral solutions, *i.e.*, the form in which most biological products historically have been approved. Although the

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19 *See Amgen v. Sandoz*, 877 F.3d 1315, 1320 (Fed. Cir. 2017) (noting that BPCIA “has certain similarities in its goals and procedures to the [Hatch-Waxman Act],” although it also has several obvious differences).
term was not explicitly defined in either the statute or FDA’s implementing regulations. FDA defined the term precisely in its publication Approved Drug Products With Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. The Orange Book is a highly relevant source for ascertaining FDA’s definition of “strength” for purposes of the Hatch-Waxman Act because it is the only Agency publication specifically referenced in the Hatch-Waxman Act. See 21 U.S.C. § 355(j)(7)(A). Notably, FDA regulations require the Orange Book to contain information about, among other things, the “strength” of all listed drug products. See 21 C.F.R. § 20.117(a)(3) (requiring public availability of a list of approved drugs, including the “strength”).

In the Orange Book, FDA defined the “strength” of parenteral drug products, including both injectable solutions and dry solids, as follows:

The strength of parenteral drug products is defined as the total drug content of the container.

Orange Book, p. xvii (29th ed. 2009) (emphasis added) (Exhibit 4). FDA adopted this clear and unambiguous definition in 2003 – more than six years before passage of the BPCIA. FDA maintained that definition in the Orange Book, without revision, for approximately 12 years, until 2016. See, e.g., Orange Book, p. xvii (23rd ed. 2003) (Exhibit 5); Orange Book, p. xvii (35th ed. 2015) (Exhibit 6). Significantly, this spanned the period during which Congress considered and passed, and the President signed, the BPCIA, which is the relevant time for determining Congressional intent.21

Notably, the above definition of strength does not include or account for “concentration.” This omission was intentional. FDA explained that prior to 2003, the Orange Book displayed only the concentration of a parenteral drug product (e.g., 5 mg/mL), not its “strength.” Orange Book, p. xvii (2009). FDA sought to correct that oversight beginning in 2003, explaining that “[w]ith the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug, it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution.” Orange Book, p. xvii (2009).

20 FDA’s cGMP regulations have long contained a definition of “strength,” see 21 C.F.R. § 210.3(b)(16), but it is a highly specialized definition that applies solely to cGMP issues, id. § 210.3(b) (limiting applicability of definitions to cGMP regulations). Consequently, it is not relevant for purposes of defining “strength” in the context of the Hatch-Waxman Act or the BPCIA.

21 MCI Telecomms. Corp. v. AT&T Co., 512 U.S. 218, 228 (1994) (identifying the time of enactment as “the most relevant time for determining a statutory term’s meaning”); Rouse v. Wachovia Mort., FSB, 747 F.3d 707, 714 (9th Cir. 2014) (“In interpreting Congressional intent, we look to the time of Congress’s enactment of the legislation.”). Moreover, although there are some FDA statements indicating that a change in concentration may be considered a change in strength (e.g., FDA Response to Sterling Winthrop Petition, Docket No. 92P-0224 (Sept. 11, 1992); FDA Response to OFW Petition, FDA-2004-P-0418 (June 19, 2012)), these all appear to have been made either prior to FDA’s 2003 changes to the Orange Book or after passage of the BPCIA. Accordingly, they are not relevant for purposes of determining Congressional intent at the time the BPCIA was enacted. In any event, they do not override the clear and unequivocal statements made in the Orange Book, which would have been the most conspicuous and authoritative evidence of the definition of “strength” available to Congress at that time.
Accordingly, around 2003, FDA began displaying the strength of parenteral drug products – the total drug content per container – in addition to the concentration (e.g., 1Gm/20mL (50mg/ml)). FDA continued to display the concentration of parenteral solutions in accordance with its past practice, while making clear that concentration was not a component of the “strength” of such drugs; rather, under the Hatch-Waxman Act, the strength of a parenteral drug was limited to the total drug content of the relevant container. See Orange Book, p. xvii (2009) (“Until recently the strength of liquid parenteral drugs products in the Orange Book have not been displayed[,]” only the concentration.). Consequently, the 2003 update to the Orange Book does not represent a change in FDA’s longstanding position regarding the strength of parenteral solutions; it simply represents the correction of a longstanding error in how strength was displayed for such products.

The well-settled meaning of “strength” as “total drug content” is further confirmed by updates to the United States Pharmacopeia (“USP”) implemented during the period leading to enactment of the BPCIA to address the risk of medication errors for parenteral drug products. Indeed, FDA’s modernization of the Orange Book in 2003 appears to have been driven, in part, by the same safety concerns that prompted changes to the USP. Prior to 2003, the labeling for many parenteral drugs identified only the concentration (mg/mL) (consistent with Orange Book listings). However, the expression of concentration often was misunderstood by physicians and patients to mean the total drug content of the container. This confusion resulted in dosing errors (e.g., overdoses) and reports of serious adverse events. To address this situation, the USP Safe Medication Use Expert Committee proposed changes to the expression of strength in the labeling of certain parenteral drugs in 2005.

These changes ultimately were approved in 2007 as a new subsection within General Chapter <1> applicable to parenteral drugs, which became official in 2009. This section required labeling to identify the strength per total volume as the primary and prominent expression on the principal display panel, followed by the concentration (mg/mL). Strength, in turn, was defined as “total drug content.” By this revision, the USP sought to draw clear distinctions between “strength” (total drug content), total volume, and concentration (mg/mL) and to ensure that the actual strength of a parenteral drug product was clearly and prominently identified on its labeling. This revision was proposed and adopted prior to enactment of the BPCIA.


24 USP, General Chapter <1>, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products (Vol. 31 2009) (Exhibit 9).
The D.C. Circuit has instructed that “words are to be read in the context in which they are used and in the broader context of the statutory scheme.” Consequently, when Congress uses a term of art, courts generally assume that “Congress intended it to have its established meaning.” In other words, “[w]hen Congress uses a term with a settled meaning, its intent is clear for purposes of Chevron step one.

This rule applies with special force when Congress borrows language from another statute. According to the Supreme Court, “when administrative and judicial interpretations have settled the meaning of an existing statutory provision, repetition of the same language in a new statute indicates, as a general matter, the intent to incorporate its administrative and judicial interpretations as well.” In other words, “if a word is obviously transplanted from another legal source, whether the common law or other legislation, it brings the old soil with it.”

The regulatory history demonstrates that when the BPCIA was enacted, “strength” was a term of art with a long-standing, unequivocal meaning under the Hatch-Waxman Act: “The strength of parenteral drug products is defined as the total drug content of the container.” Orange Book, p. xvii (29th ed. 2009) (emphasis added) (Exhibit 4). The meaning of “strength” was transplanted root and branch from the Hatch-Waxman Act into the BPCIA; it therefore must be presumed to retain the established meaning it had at that time under the Hatch-Waxman Act. Consequently, for Chevron step one, “strength” is clear and unambiguous and means the “total drug content” of a parenteral solution, without regard to concentration.

b. FDA’s Current Interpretation of “Strength” Is Foreclosed By the Clear Statutory Text

“Strength” and “concentration” had distinct, non-overlapping meanings when the BPCIA was enacted. And Congress omitted the term “concentration” from the BPCIA. The FDA’s current interpretation of “strength” to include concentration therefore conflicts with the BPCIA’s clear statutory text.

25 Ass’n Civilian Technicians, Inc. v. United States, 603 F.3d 989, 992 (D.C. Cir. 2010); see also United States v. Wilson, 290 F.3d 347, 356 (D.C. Cir. 2002), cert. denied, 537 U.S. 1028 (2002) (“Congress is presumed to preserve, not abrogate, the background understandings against which it legislates.”).

26 McDermott Int’l, Inc. v. Wilander, 498 U.S. 337, 342 (1991); see also FAA v. Cooper, 566 U.S. 284, 292 (2012) (“when Congress employs a term of art, ‘it presumably knows and adopts the cluster of ideas that were attached to each borrowed word in the body of learning from which it was taken’” (citations omitted)); Stat-Trade, Inc., 869 F. Supp. 2d 95, 106-07.

27 Grace v. Whitaker, 344 F. Supp. 3d 96, 128 (D.D.C. 2018); see also Stat-Trade, 869 F. Supp. 2d 95, 106-07 (“interpreting the term “same product” as used in the Prescription Drug User Fee Act to incorporate the ANDA sameness requirement from the Hatch-Waxman Act” for purposes of Chevron step one analysis).

28 Bragdon v. Abbott, 524 U.S. 624, 645 (1998); see also Grace, 344 F. Supp. 3d at 128 (“Congress is presumed to have incorporated prior administrative and judicial interpretations of language in a statute when it uses the same language in a subsequent enactment.”).

FDA is bound by the meaning of unambiguous terms. When Congress referenced “strength” – but not “concentration” – in the BPCIA, it must be presumed to have known the well-established difference between these regulatory concepts and to have acted purposefully in rejecting any “same concentration” requirement for parenteral solutions. As courts have noted, “Congress is presumed to preserve, not abrogate, the background understandings against which it legislates.”

Even where Congress has “established an ambiguous line, the agency can go no further than the ambiguity will allow.” A “judicial decision concluding that a statutory term admits of some ambiguity does not open the door at Chevron step one for purposes of all interpretations.” “[W]here the text and reasonable inferences from it give a clear answer against the government . . . that . . . is the end of the matter” under Chevron step one. In other words, “the Court must consider whether the statute ‘unambiguously forbids the Agency’s interpretation.’” Here, when read in context and using the traditional tools of statutory construction, the BPCIA unambiguously forbids FDA’s interpretation of “strength” to mean not just total drug content, but also concentration, for injectable solutions. Even if “strength” were ambiguous in some contexts (e.g., as applied to patches with reservoirs), that does not change its unambiguous meaning in the context of injectable solutions.

The most forceful evidence of this Congressional intent comes from FDA itself. As addressed above, before the BPCIA was enacted, FDA changed the way drug information was listed and labeled in the Orange Book, adding “strength” to the already listed “concentration” to avoid confusion. In the context of parenteral drugs, FDA thus specifically rejected the idea that the “strength” of a parenteral solution encompasses its “concentration,” instead treating them as two different, freestanding regulatory concepts.

This distinction between “strength” and “concentration” was further reinforced by several FDA regulations and guidance documents that were operative during the relevant period. For example, FDA regulations governing National Drug Codes (“NDC”) required sponsors to obtain a new NDC number if there was any change in “strength or concentration.” Likewise, the preamble to the 2009 Orange Book defined “pharmaceutical equivalents” to mean drug products that are, inter alia, “identical in strength or concentration.”

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30 Wilson, 290 F.3d at 356.


32 Id. at 208 (emphasis in original).

33 Id. at 208 (citing Cal. Indep. Sys. Operator Corp. v. FERC, 372 F.3d 395,401 (D.C. Cir. 2004)).

34 Id. (citing Barnhart v. Walton, 535 U.S. 212, 218 (2002)).
product within a single New Drug Application. FDA’s bioequivalence regulations also treated “strength” and “concentration” as separate regulatory concepts. Although these references to “strength or concentration” were not specific to parenteral solutions, they reinforce the distinction between “strength” and “concentration” that FDA identified in 2003 when it began listing the “strength” of parenteral solutions in the Orange Book.

Finally, this conclusion is strengthened by a comparison of the structure and purpose of the Hatch-Waxman Act and the BPCIA. Significantly, the Hatch-Waxman Act has never explicitly required any drug (including a parenteral drug) to have the “same concentration” of active ingredients as the reference listed drug (“RLD”) – only the same “strength.” 21 U.S.C. § 355(j)(2)(A)(iii). Although FDA’s implementing regulations impose a “same concentration” requirement for parenteral drugs, this requirement applies solely to inactive ingredients. 21 C.F.R. §§ 314.94(a)(9)(iii), 314.127(a)(8)(ii)(B). Therefore, prior to recent regulatory changes enacted in 2016, there was no “same concentration” requirement in either the Hatch-Waxman Act or its implementing regulations for active ingredients.

In the BPCIA, Congress was even more lenient with respect to concentration, explicitly rejecting any requirement that a follow-on product – even a parenteral product – must have the same inactive ingredients in the same concentration as the RP (i.e., to be Q1/Q2 the same as the RP). Instead, a biological product approved via the 351(k) pathway may be “highly similar” to the RP, permitting “minor differences in clinically inactive components.” 42 U.S.C. §§ 262(i)(2)(A), (k)(2)(A)(i)(I)(aa). FDA has interpreted this provision appropriately to mean that formulation differences between a proposed biosimilar or interchangeable product and the RP, including differences in the identity or concentration of inactive ingredients, may be acceptable under section 351(k). See FDA, Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1), p. 5 (Dec. 2018) (Exhibit 10).

FDA may not now incorporate a “concentration” requirement into the definition of “strength” for parenteral solutions regulated under the BPCIA. Because any “same concentration” requirement under the Hatch-Waxman Act is based entirely on FDA regulations governing inactive ingredients, and because the BPCIA explicitly rejects any requirement that biosimilar or interchangeable biological products must have the same concentration of inactive ingredients as the RP, the BPCIA cannot now be read to require, either directly or indirectly, parenteral biological products to have the same concentration of active or inactive ingredients as the RP. FDA’s attempt to import a “same concentration” requirement into the definition of “strength” thus is foreclosed by the clear statutory language and structure of the BPCIA.

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36 Compare 21 C.F.R. § 320.22(b)(1)(ii) (allowing waiver of in vivo bioequivalence testing for parenteral drugs with the same active and inactive ingredients in the same concentration as the RLD), with 21 C.F.R. § 320.22(d)(2) (allowing waiver of in vivo BE testing for different strengths).
c. FDA’s New Regulation Defining “Strength” Is Irrelevant

In 2016, FDA promulgated revised Hatch-Waxman regulations that, for the first time, defined the term “strength.” 81 Fed. Reg. 69580 (Oct. 6, 2016). Although “strength” is now defined to include, in some cases, “concentration,” this post hoc regulatory revision does not and cannot change the meaning of the statutory term adopted by Congress in the BPCIA in 2010. As such, the new regulatory definition is irrelevant to the meaning of the term “strength” for Chevron step one purposes.

The 2016 regulation defines “strength” as “the amount of drug substance contained in, delivered, or deliverable from a drug product.” 21 C.F.R. § 314.3. The regulation further states that this includes: (i) “The total quantity of drug substance in mass or units of activity in a dosage unit or container closure . . . and/or, as applicable,” (ii) “The concentration of the drug substance in mass or units of activity per unit volume or mass.” Id. 37 In 2016, FDA also revised the Orange Book to be consistent with this new regulation: “[t]he strength of parenteral drug products generally is identified by both the total drug content and the concentration of drug substance in a container approved by FDA.” Orange Book, p. xvi (36th ed. 2016).

FDA’s new definition of strength is irrelevant to the Chevron step one analysis for several reasons. First, a post hoc regulatory change cannot affect the meaning of a statutory term adopted by Congress more than five years before promulgation of the new regulation. It is a well-established rule of statutory construction that in interpreting Congressional intent, courts must “look to the time of Congress’s enactment of the legislation.” 38 Indeed, the Supreme Court has instructed that “the most relevant time for determining a statutory term’s meaning” is the time of enactment. 39 For this reason, courts “do not rewrite legislation in light of changed circumstances.” 40 Accordingly, the 2016 regulation has absolutely no bearing on the meaning of “strength” in the 2010 BPCIA. The statutory meaning of that term prevails for parenteral solutions regulated under the BPCIA. 41 For the reasons discussed above, the clear statutory meaning of the term “strength” as applied to parenteral solutions is “total drug content” without regard to concentration.

37 FDA asserted that this new definition of strength simply codified the Agency’s “longstanding use” of the term. 80 Fed. Reg. 6802, 6809 (Feb. 6, 2015). This assertion, however, is contradicted by how “strength” was defined in the Orange Book for more than a decade (from 2003 through 2015) to mean a parenteral drug’s “total drug content” and not its concentration, as documented in sections II.B.2.a and II.B.2.b above.

38 Rouse, 747 F.3d 707, 714; see also St. Francis College v. Al-Khazraji, 481 U.S. 604, 610 (1987), reh’g denied, 483 U.S. 1011 (1987) (interpreting “race” in accordance with its meaning when the law was enacted rather than according to modern usage).

39 MCI, 512 U.S. 218, 228; see also Bostock v. Clayton Cty., 2020 U.S. LEXIS 3252, *12 (June 15, 2020) (“This Court normally interprets a statute in accord with the ordinary public meaning of its terms at the time of its enactment.”) (emphasis added); Carceri, 555 U.S. at 393 n.8 (noting the Court’s disagreement with Justice Stevens’ dissenting opinion argument that a term’s meaning is “controlled by later-enacted regulations”).

40 Rouse, 747 F.3d 707, 714.

41 See Stat-Trade, 869 F. Supp. 2d 95, 105 (rejecting new Agency interpretation of statutory term as inconsistent with the clear statutory language).
Second, by its own terms, the regulation does not apply to biological products subject to licensing under the PHS Act. 21 C.F.R. § 314.1(b). Thus, the definition of “strength” set forth in the revised Hatch-Waxman regulations is simply irrelevant to the subject of this petition – biological products seeking BLA approval via the 351(k) pathway.

3. FDA’s Interpretation of Strength Is Unreasonable (Chevron Step Two)

Even if the term “strength” were ambiguous in the context of parenteral solutions (which it is not), FDA’s interpretation nevertheless would be impermissible under step two of the Chevron test because it is unreasonable. The FDA’s interpretation can survive Chevron step two only if the Agency provides “a reasonable explanation for how its interpretation serves the statute.” Here, FDA’s interpretation subverts the goals of the BPCIA in at least two ways. First, FDA’s interpretation facilitates and encourages anti-competitive evergreening tactics designed to prevent or delay competition from biological products seeking approval under the 351(k) pathway, contrary to the intent of the BPCIA. Second, FDA’s interpretation serves to undermine the BPCIA’s goal of speeding the development of biosimilar and interchangeable biological products, with no legitimate countervailing regulatory purpose. Because FDA’s interpretation undermines the underlying goals of the BPCIA rather than serves them, it is unreasonable under Chevron step two.

a. FDA’s Interpretation Facilitates Anti-Competitive Evergreening Tactics

FDA’s interpretation fails step two of the Chevron test because it permits and encourages anti-competitive evergreening tactics by certain brand sponsors. Because this undermines one of the core goals of the BPCIA – to facilitate increased competition by biosimilar and interchangeable biological products – FDA’s interpretation is unreasonable.

Like the Hatch-Waxman Act upon which it was modeled, “the BPCIA was designed to foster both price competition and innovation in the field of biologics.” To encourage innovation, the BPCIA provides four- and twelve-year exclusivity periods to RPs. To protect “consumer interests,” the BPCIA creates an abbreviated approval pathway, much like the generic drug approval pathway under the Hatch-Waxman Act, to encourage the development of lower-cost, safe and effective biological products. Thus, one of the primary goals of the BPCIA is to spur competition among biological products and thereby increase access to affordable biological products by patients in the United States. Indeed, “Price Competition” is part of the Act’s popular name.

FDA’s interpretation of “strength” to include “concentration,” however, undermines this core BPCIA goal by facilitating anti-competitive evergreening tactics. Specifically, FDA’s

42 Braeburn, 389 F. Supp. 3d 1, 23.

43 Genentech, Inc. v. Amgen, Inc., 2020 U.S. Dist. LEXIS 23311 (D. Del. Feb. 11, 2020); see also BPCIA, Pub. L. No. 111-148, § 7001(b) (2010) (“It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established.”); Amgen, 877 F.3d 1315, 1320 (noting that the BPCIA and Hatch-Waxman Act have similar goals, including balancing “innovation and price competition”).
interpretation allows brand biologic manufacturers to avoid competition from biological products seeking approval via the 351(k) pathway by making insignificant changes to the RP’s concentration that have no impact on the therapeutic safety or effectiveness of such products. To state the most extreme example, under the FDA’s interpretation, a brand biologic manufacturer could add or remove *a single drop of water* to its product and thereby block approval of a 351(k) application for a competing product. Moreover, this tactic could be employed as soon as a 351(k) application is approved – or even submitted – to delay, prevent the licensure of, or circumvent the effect of a biosimilar or interchangeable designation in the marketplace.

This tactic is particularly damaging to biosimilar and interchangeable biological products because of the high costs and extended time needed to develop such products. In 2009, the Federal Trade Commission (“FTC”) estimated that it likely would take eight to ten years to develop a biosimilar medication, with an estimated development cost of between $100 and $200 million. In Boehringer Ingelheim’s experience, these estimates are, if anything, conservative. Moreover, the development of biological products under the 351(k) pathway requires substantial fixed costs because of the complex manufacturing processes and controls needed to produce biological products. These costs and timelines differ substantially from those of small-molecule generic drugs, which typically take three to five years to develop and cost between $1 and $5 million.

When FDA interprets “strength” to mean concentration, it allows brand manufacturers to manipulate the concentration of their RPs during the extended eight to ten-year development period for biosimilars. When timed strategically, this unfairly creates a “moving target” for sponsors seeking approval via the 351(k) pathway. Because of the huge investment of time and resources needed to develop a biosimilar, sponsors of such products cannot easily match serial concentration changes of the RP and thus may be more susceptible to these anti-competitive tactics than their generic counterparts.

The burden of this tactic falls not just on biosimilar sponsors but also, more importantly, on the patients who need and use these critical biological medications. Biological medications have become increasingly important in recent years for treating a wide variety of serious and life-threatening diseases, and they hold great promise for delivering future therapies to patients in need. Yet biological products also represent some of the most expensive medications to patients and the healthcare system as a whole. The BPCIA was intended to decrease the costs of these critical medications to patients by encouraging increased accessibility and price competition from biological products approved via the 351(k) pathway. By encouraging tactics that can be used to delay or block approval of competing products via the 351(k) pathway, however, FDA’s interpretation of “strength” prevents patients from having access to lower-cost biological products, contrary to the intent of the BPCIA.

These concerns are far from speculative. Some brand companies have engaged in a wide range of anti-competitive tactics to impede competition from biosimilar products, including abuse

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of the Risk Evaluation and Mitigation Strategy ("REMS") requirements\(^\text{45}\) and the dissemination of false and misleading information about biosimilars,\(^\text{46}\) and there is no reason to assume these tactics will stop in the future.

Congress was acutely aware of these types of evergreening tactics when it enacted the BPCIA and thus included provisions specifically designed to prevent the most obvious schemes. For example, Congress was careful to ensure that the BPCIA exclusivity provisions could not be used anti-competitively to evergreen the extremely generous 12-year exclusivity period for minor product changes. The BPCIA thus provides that the exclusivity protections are available only to the first licensure of an RP and not to product changes effected through, \textit{inter alia}, a supplement, such as changes to a product’s concentration. 42 U.S.C. § 262(k)(7)(C).

Here, by contrast, FDA’s interpretation of “strength” encourages a new evergreening tactic: manipulation of the concentration of an RP. By changing the concentration of the RP at strategic moments, and then aggressively switching patients to the new product, brand sponsors can avoid direct competition from products that are biosimilar or interchangeable to the previous concentration. Worse, this product hopping tactic can be accomplished through concentration changes as insignificant as the addition or removal of a single drop of water. These concentration manipulations will be particularly damaging to proposed interchangeable products, since much of their unique value to patients and the healthcare system as a whole stems from the fact that they can be substituted for the brand without the knowledge or approval of the prescribing health care practitioner, much like generic drugs. Once a concentration change is implemented, however, this interchangeability status will be automatically lost under FDA’s current policy, along with the significant cost savings intended by Congress.

If FDA interprets strength to mean “total drug content” without regard to concentration, as intended by Congress, these types of evergreening and product-hopping tactics would be much more difficult to accomplish.\(^\text{47}\) Because this type of anti-competitive “game-playing” is antithetical to the intent and goals of the BPCIA, FDA’s interpretation – which facilitates this new tactic – is unreasonable under step two of the \textit{Chevron} test.


\(^\text{46}\) See Joint Statement of the Food & Drug Administration and the Federal Trade Commission Regarding a Collaboration to Advance Competition in the Biologic Marketplace, p. 3 (Feb. 3, 2020) (“Both FDA and FTC support competitive markets for biologics and have serious concerns about false or misleading statements and their negative impacts on public health and competition.”); see also Pfizer Citizen Petition, Docket No. FDA-2018-P-3281 (Aug. 22, 2018) (requesting FDA action to stop false and misleading representations about RPs and biosimilars).

\(^\text{47}\) Interpreting “strength” to mean “total drug content” would not create unexpected evergreening problems with respect to RP exclusivity. The BPCIA contains a list of changes for which exclusivity cannot be granted (\textit{e.g.}, strength, route of administration, indication). 42 U.S.C. § 262(k)(7)(C)(ii)(I). Although the list does not explicitly mention “concentration,” FDA could require changes to the concentration of a RP to be implemented via a supplement, as was done with Humira HC. This solution would avoid potential evergreening concerns while simultaneously encouraging robust price competition.
b. **FDA’s Interpretation Prevents Licensure of Biological Products That Are Biosimilar to or Interchangeable With the RP**

FDA’s interpretation also fails step two of the *Chevron* test because it undermines the BPCIA’s goal of speeding the development and availability of biosimilar and interchangeable biological products, with no legitimate countervailing regulatory purpose. Specifically, FDA’s interpretation prevents a biological product with the same total drug content but a different concentration than the RP from being licensed as a biosimilar or interchangeable biological product *even if the proposed product meets all statutory requirements for a biosimilarity or interchangeability determination* (i.e., all requirements aside from FDA’s unreasonable interpretation of “strength”). By limiting the availability of biosimilarity and interchangeability determinations in this mechanical and categorical manner, FDA’s interpretation impairs price competition and access to affordable biological products, contrary to the intent of the BPCIA.

In many cases, injectable products having the same total drug content but different concentrations exhibit no differences in safety, effectiveness, operation, or directions for use.\(^{48}\) This is particularly the case where the entire content of a unit, such as a vial, is administered in a single dose and/or the biological product is administered via a dosing device, such as a prefilled syringe or pen injector. The patient receives the full dose upon injection of the entire unit, and the relevant issue from the clinical perspective is the total amount of active ingredient injected, not the specific concentration of the aqueous drug product prior to injection. In such a case, minor differences in concentration often are not clinically meaningful.

Boehringer Ingelheim believes this is the case with many biological products formulated as parenteral solutions where the strength (total drug content), dosing regimen, route of administration, and method of delivery (including dosing instructions) are the same. For example, although the currently approved adalimumab products have a relatively higher injection volume than Humira HC, the absolute difference is minimal – a maximum of just 0.4 mL – and is attributable to clinically inactive components. This minimal difference is not likely to be meaningfully perceptible to a patient or healthcare provider or to result in meaningful differences in directions for use. Indeed, the labeling for the OC and HC Humira pens recommends the same 10 second duration of injection. More significantly, patients using any of the adalimumab biosimilars will get the same total drug content as Humira HC.

Nevertheless, FDA’s interpretation of “strength” to necessarily include content and concentration for all parenteral solutions categorically prevents Cyltezo and other OC adalimumab products from being considered biosimilar to or interchangeable with Humira HC. Specifically, it prevents biosimilarity and interchangeability determinations for products with the same total drug content but different concentrations *even if* the proposed product meets all applicable statutory requirements in that it:

1. Is “biosimilar to the reference product” as demonstrated by analytical, animal, and/or clinical testing;

\(^{48}\) See, e.g., Comment of Novartis, FDA-2011-D-0611-0020, pp. 13-14 (April 13, 2012); Comment of Teva Pharmaceuticals, p. 4 (April 20, 2012) (impact of concentration differences is “often negligible”).
2. Can be “expected to produce the same clinical result as the reference product in any given patient;” and

3. Does not present greater risks in terms of safety or diminished efficacy from alternating or switching.


This is not only unreasonable but also unnecessary. If a concentration difference presents real safety or efficacy concerns, the BPCIA provides more calibrated mechanisms than the “same strength” requirement for FDA to identify and address them. For example, FDA can refuse to license a biological product as biosimilar or interchangeable if concentration differences are so significant that the proposed product does not meet the relevant biosimilarity requirements. Id. §§ 262(k)(2)(A)(i)(I)(aa), (k)(4)(A)(i). This could occur, for example, if the concentration difference is so significant as to preclude a finding of “highly similar” to the RP notwithstanding minor differences in clinically inactive components or results in “clinically meaningful differences” between the products. Id. §§ 262(i)(2)(A), (B). FDA also could refuse to license a proposed product as interchangeable if concentration differences prevent the sponsor from demonstrating that the proposed product could be expected to produce the same clinical result as the RP in any given patient because of, for instance, different or more frequent adverse events. Id. § 262(i)(4)(A)(ii).

FDA should be able to assess the clinical effects of concentration differences, if any, via the usual analytical and clinical studies required to demonstrate biosimilarity and interchangeability. Significantly, this calibrated approach would distinguish between products that, despite minor concentration differences, have no clinically meaningful differences from the RP and/or may be substituted for the RP without the intervention of the prescribing physician, and those that cannot. Indeed, FDA’s treatment of lyophilized powders (discussed further below) demonstrates that FDA can adequately address the clinical effect of concentration differences through these other BPCIA mechanisms without relying on a blunt instrument like the definition of strength. In contrast, FDA’s current interpretation completely forecloses licensure of biosimilar and interchangeable products with concentration differences from the RP, even if they could be proven to have no clinically meaningful differences in terms of safety, purity or potency than the RP.

In sum, because FDA’s interpretation of “strength” places an artificial and unnecessary limitation on certain products eligible for approval via the 351(k) pathway, it undermines the BPCIA’s core goal of encouraging price competition through the timely approval of biosimilar and interchangeable biological products. As such, it is unreasonable under step two of the Chevron test.
4. **FDA’s Interpretation of “Strength” Is Arbitrary and Capricious in Violation of the Administrative Procedure Act (APA)**

Finally, FDA’s interpretation of strength is arbitrary and capricious in violation of the APA, 5 U.S.C. § 706(2)(A), because it treats injectable solutions differently than similarly situated parenteral products without a legitimate reason. The federal courts have consistently recognized that “an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.”\(^{49}\) In *Bracco Diagnostics v. Shalala*, the seminal case involving FDA-regulated products, the court set aside FDA’s regulation of ultrasound contrast agents because the Agency was “applying very different standards to assess the safety and effectiveness of essentially identical products.”\(^{50}\) The court noted that treating similarly situated parties differently is “arbitrary and capricious in violation of the APA.”\(^{51}\)

Here, FDA is treating injectable solutions differently than similarly situated parenteral products for purposes of defining “strength.” For example, FDA’s longstanding and continuing practice is to treat the “strength” of a lyophilized powder (intended for reconstitution and parenteral injection) as the total drug content in the container, without regard to the concentration after reconstitution. FDA took this position in the Hatch-Waxman context at least as early as 2003, when it explained in the Orange Book preface that “The amount of dry powder or freeze dried powder in a container has always been identified as the strength.” Orange Book, Preface (2003) (Exhibit 5). The current version of the Orange Book uses similar language: “Generally, the amount of dry powder or lyophilized powder in a container is identified as the strength, expressed as x mg/vial.” Orange Book, p. xvii (40th ed. 2020) (Exhibit 11).

Significantly, FDA is applying this same definition of strength (total drug content) to dry/lyophilized powders regulated as biologics under the BPCIA. Although FDA initially proposed to take concentration into account for such products (see discussion in section II.A.2 above), the Agency reversed course in 2018. In the 2018 Draft Q&A Guidance, FDA now takes that position that, in general, “for a proposed biosimilar product or proposed interchangeable product that is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, a sponsor can demonstrate that the product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity).” 2018 Draft Q&A Guidance, p. 5 (Exhibit 3). Although FDA recommends that a lyophilized powder should have the same concentration as the RP when reconstituted, it acknowledges that this is “not a part of demonstrating same ’strength.’” 2018 Draft Q&A Guidance, p. 5 (emphasis added). Consequently, when determining “strength,” FDA

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\(^{49}\) *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997); see also *Indep. Turtle Farmers of La. v. United States*, 703 F. Supp. 2d 604, 625 (W.D. La. 2010) (remanding in part because FDA failed to explain why plaintiff’s “contentions that other pets and food products could also present a risk of contamination” should be treated differently); *United States v. Diapulse Corp. of Am.*, 748 F.2d 56, 62 (2d Cir. 1984) (“[W]e must insist that the FDA apply its scientific conclusions evenhandedly and that it not ‘grant to one person the right to do that which it denies to another similarly situated.’”).

\(^{50}\) *Bracco Diagnostics*, 963 F. Supp. at 24.

\(^{51}\) *Id.* at 28.
treats dry powders intended for reconstitution and injection differently than injectable products already in a solution dosage form.

This disparate treatment of similarly situated, parenteral products is not justified. Although lyophilized powders and ready-to-use injectable solutions are considered to be different dosage forms, they nevertheless are similarly situated for purposes of strength determinations under the BPCIA because they both are intended to be administered to patients in solution as an injection. There is thus no basis from a safety or effectiveness perspective for FDA to consider “concentration” to be a relevant consideration for one parenteral product but not the other—and thus no basis for treating them differently with respect to strength determinations. Because there is no legitimate explanation for FDA’s disparate treatment, its interpretation of strength is arbitrary and capricious in violation of the APA. 5 U.S.C. § 706(2)(A).

5. **As a Matter of Discretion, FDA Should Interpret Strength to Mean Total Drug Content Without Regard to Concentration**

Finally, even assuming the text and structure of the BPCIA do not compel the result that Boehringer Ingelheim seeks here (which they do), the Agency nevertheless should change its interpretation as a matter of discretion.

No statute or regulation mandates that FDA consider concentration in determining a parenteral biological product’s strength. This is demonstrated by FDA’s shifting treatment of dry solids intended for reconstitution and injection (see section II.B.4 above). Therefore, even if FDA disagrees that the BPCIA imposes an obligation to define “strength” without reference to concentration for parenteral biological products, including parenteral solutions, at the very least, FDA has discretion to do so. Boehringer Ingelheim submits FDA should exercise that discretion to change its current interpretation of “strength.”

Defining “strength” based on total drug content alone would accomplish several important objectives, including: (1) preventing abusive evergreening and product hopping tactics from stifling competition from affordable biosimilar and interchangeable biological products; (2) encouraging price competition through the timely approval of biosimilar and interchangeable biological products, and (3) maintaining fair and consistent treatment of all similarly situated parenteral biological products. Even if FDA does not consider these factors determinative under *Chevron* step two or the APA’s “arbitrary and capricious” legal standard, they nevertheless are persuasive reasons for FDA to exercise its discretion to interpret the “strength” of parenteral solutions regulated under the BPCIA to mean “total drug content” without regard to concentration.

Moreover, to Boehringer Ingelheim’s knowledge, there are no persuasive countervailing regulatory interests that outweigh the above factors. As noted above, any clinical effects of concentration differences would be identified and addressed through the BPCIA’s more calibrated approval requirements rather than through a blunt instrument like the definition of strength. Moreover, interpreting “strength” to mean “total drug content” would not create unexpected evergreening problems with respect to RP exclusivity because FDA could take simple, regulatory steps to avoid such problems (see footnote 47). Finally, there would be no negative effect on the post-market safety of affected products since this change in policy would not require any
modifications in how parenteral solutions are labeled or how adverse experiences are reported or handled. On the contrary, parenteral solutions would continue to be labeled with the strength (total drug content), total volume, and concentration per FDA guidance and USP monograph standards. Consequently, the total volume and concentration could continue to be used to identify, report, and assess suspect products for purposes of post-market safety reporting, and other identifiers also would continue to be used to identify the suspect product (e.g., trade name, NDC number, lot number, etc.). See 21 C.F.R. 600.80(f)(1); see also FDA Form 3500A (2/19). The only difference is that total volume and concentration would no longer be relevant factors in determining the “strength” of a parenteral solution for purposes of section 351(k) of the PHS Act, 42 U.S.C. § 262(k).

Because interpreting “strength” to mean “total drug content” best serves the goals of the BPCIA, there are no countervailing regulatory interests that outweigh this benefit, and no statute or regulation mandates a different definition, FDA should exercise its discretion to change its current interpretation of “strength” as applied to parenteral solutions.

C. Conclusion

For the reasons above, FDA’s current interpretation of “strength” as applied to parenteral solutions is invalid as a matter of both law and policy. It conflicts with the clear language of the BPCIA, undermines the BPCIA’s goal of speeding the development of biosimilar and interchangeable biological products, with no legitimate countervailing regulatory purpose, and arbitrarily treats parenteral solutions differently than similarly situated parenteral products (e.g., lyophilized powders). Accordingly, Boehringer Ingelheim respectfully requests that FDA (1) interpret the term “strength” to mean the total drug content of a parenteral biological product, without regard to concentration; (2) revise relevant guidance documents to conform to this interpretation; and (3) implement this interpretation immediately in the Agency’s review of new and pending 351(k) applications, supplements, and amendments. Boehringer Ingelheim believes these actions will benefit patients and the healthcare system as a whole by increasing access to more affordable biological products approved via the 351(k) pathway.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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cc: Elizabeth H. Dickinson, J.D.
Eva Temkin, J.D.

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Exhibits

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53 Boehringer Ingelheim is not submitting the certification set forth in 21 C.F.R. § 10.31(c) because the action requested in this petition, if taken, could not delay approval of any ANDAs, 505(b)(2) applications or 351(k) applications. See 21 C.F.R. § 10.31(a)(1). Boehringer Ingelheim, in fact, believes granting this petition would have the opposite effect.
EXHIBIT 1
Guidance for Industry


DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD  20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

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.
Guidance for Industry


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Biosimilarity
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>QUESTIONS AND ANSWERS</td>
<td>4</td>
</tr>
<tr>
<td>I. BIOSIMILARITY OR INTERCHANGEABILITY</td>
<td>4</td>
</tr>
<tr>
<td>II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A &quot;BIOLOGICAL PRODUCT&quot;</td>
<td>12</td>
</tr>
<tr>
<td>III. EXCLUSIVITY</td>
<td>15</td>
</tr>
</tbody>
</table>
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.

INTRODUCTION

This guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA’s interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The questions and answers (Q&As) are grouped below in the following categories:

- Biosimilarity or Interchangeability
- Provisions Related to Requirement to Submit a BLA for a “Biological Product”
- Exclusivity

The BPCI Act amends the Public Health Service Act (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)). On November 2 and 3, 2010, FDA held a public hearing and established a public docket to obtain input on specific issues and challenges associated with the implementation of the BPCI Act (see Docket No. FDA-2010-N-0477). This guidance describes FDA’s current interpretation of certain statutory requirements added by the BPCI Act and reflects consideration of the comments concerning those requirements that were submitted to the public docket.

1 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.
This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act. The guidances address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

When applicable, references to information in these guidances are included in this Q&A guidance.

The Q&A format is intended to promote transparency and facilitate development programs for proposed biosimilar products by addressing questions that may arise in the early stages of development. In addition, these Q&As respond to questions the Agency has received from prospective BLA and new drug application (NDA) applicants regarding the appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance to include additional Q&As as appropriate.²

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

**BACKGROUND**

The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the “Hatch-Waxman Act”), which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).³ The implementation of an abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger and typically more complex structure of biological products, as well as the processes by which such products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

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² The process by which FDA is requesting public comment on proposed Q&As and issuing new Q&As is described in the accompanying FEDERAL REGISTER notice.

³ See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).
Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) defines biosimilarity to mean “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” (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the higher standard of “interchangeability,” an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

The BPCI Act also includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective (see section 351(k)(7) of the PHS Act);
- A 4-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted (see section 351(k)(7) of the PHS Act);
- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product (see section 351(k)(6) of the PHS Act);
- An exclusivity period for certain biological products for which pediatric studies are conducted in accordance with a written request (see section 351(m) of the PHS Act);
- A transition provision for biological products that have been or will be approved under section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020 (see section 7002(e) of the Affordable Care Act); and
- A provision stating that a 351(k) application for a biosimilar product contains a “new active ingredient” for purposes of the Pediatric Research Equity Act (PREA) (see section 505B(n) of the FD&C Act).

The BPCI Act also establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act.
QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q. I.1. Whom should a sponsor contact with questions about its biosimilar development program?

A. I.1. (Proposed Answer): If the reference product for a proposed biosimilar product is regulated by the Center for Drug Evaluation and Research (CDER), contact the Biosimilars Program Staff in CDER’s Office of New Drugs at 301-796-0700.

If the reference product for a proposed biosimilar product is regulated by the Center for Biologics Evaluation and Research (CBER), contact the Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 301-827-1800 or by email to ocod@fda.hhs.gov.

For general questions related to FDA’s implementation of the BPCI Act, contact Sandra Benton in CDER’s Office of Medical Policy at 301-796-2500.

Q. I.2. When should a sponsor request an initial meeting with FDA and what data and information should a sponsor provide to FDA as background for a proposed biosimilar development program?

A. I.2. (Proposed Answer): FDA recommends that sponsors of proposed biosimilar products request an initial meeting with FDA at such time as the sponsor can provide a proposed plan for its biosimilar development program, manufacturing process information (including planned methodology and assay validation), and preliminary comparative analytical data with the reference product.

Comparative analytical data provide the foundation for a biosimilar development program and can influence decisions about the type and amount of animal and clinical data needed. Such data should be available early in development and allow for a more detailed discussion with the Agency. FDA will best be able to provide meaningful input on the extent and scope of animal and clinical studies for a proposed biosimilar development program once the Agency has considered the comparative analytical data.

Q. I.3. Can a proposed biosimilar product have a different formulation than the reference product?

A. I.3. (Proposed Answer): Yes, differences between the formulation of a proposed product and the reference product may be acceptable. A 351(k) application must contain information demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive
components. In addition, an applicant would need to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. It may be possible, for example, for a proposed product formulated without human serum albumin to demonstrate biosimilarity to a reference product formulated with human serum albumin. For more information about FDA’s current thinking on the interpretation of the statutory standard for biosimilarity, see FDA’s draft guidances for industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product and Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

Q. I.4. **Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product?**

A. I.4. (Proposed Answer): Yes, some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled syringe or in an auto-injector device (which are considered the same “injectable” dosage form), even if the reference product is licensed in a vial presentation, provided that the proposed product meets the statutory standard for biosimilarity and adequate performance data for the delivery device or container closure system are provided. For a proposed biosimilar product in a different delivery device or container closure system, the presentation must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for certain design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

However, a prospective biosimilar applicant will not be able to obtain licensure under section 351(k) for its product when a design difference in the delivery device or container closure system results in:

- a clinically meaningful difference between the proposed product and the reference product in terms of safety, purity, and potency;
- a different route of administration or dosage form; or
- a condition of use for which the reference product has not been previously approved;

or otherwise does not meet the standard for biosimilarity.

Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, FDA may consider whether the differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients, for patients to be safely alternated or switched between the reference product.
product and one or more interchangeable products without the intervention of the prescribing healthcare provider. Additional performance data about the delivery device may also be necessary.

A proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

**Q. I.5.** Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?

A. I.5. (Proposed Answer): Yes, an applicant may obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed. An applicant must demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of safety, purity, and potency. This may include providing information from one or more studies using a route of administration for which licensure is not requested (e.g., a study using subcutaneous administration may provide a more sensitive comparative assessment of immunogenicity of the reference product and a proposed biosimilar product, even though licensure of the proposed biosimilar product is requested only for the intravenous route of administration).

**Q. I.6.** Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?

A. I.6. (Proposed Answer): Yes, an applicant is not required to obtain licensure for all presentations for which the reference product is licensed. However, if an applicant seeks licensure for a particular indication or other condition of use for which the reference product is licensed and that indication or condition of use corresponds to a certain presentation of the reference product, the applicant may need to seek licensure for that particular presentation (see also responses to Q. I.4 and Q. I.5).

**Q. I.7.** Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?

A. I.7. (Proposed Answer): Yes, a biosimilar applicant generally may obtain licensure for fewer than all conditions of use for which the reference product is licensed. The 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar product have been previously...
Q. I.8. Can a sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?

A. I.8. (Proposed Answer): Yes, a sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product. We note, however, that for certain complex biological products, a modified approach may be needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product. The type of bridging data needed likely would include a clinical PK and/or PD study conducted with the U.S.-licensed reference product.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- the relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;

- the relationship between the license holder for the non-U.S.-licensed product and BLA holder for the U.S.-licensed reference product, including whether the non-U.S.-licensed product, and/or any components thereof, are manufactured in the same facility(ies) as the U.S.-licensed reference product during the relevant time period;

- whether the non-U.S.-licensed product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries);
• whether the non-U.S.-licensed product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed; and

• the scientific bridge between the non-U.S.-licensed product and the U.S.-licensed reference product, including comparative physico-chemical characterization, bioassays/functional assays, and comparative clinical and/or nonclinical PK and/or PD data, as appropriate, and data to address any differences in formulation or primary packaging.

A sponsor also should address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

Q. I.9. Is a clinical study to assess the potential of the biological product to delay cardiac repolarization (a QT/QTc study) or a drug-drug interaction study generally needed for licensure of a proposed biosimilar product?

A. I.9. (Proposed Answer): No. In general, a proposed biosimilar product may rely upon the reference product’s clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential and drug-drug interactions.

Q. I.10. How long should sponsors retain reserve samples of the biological products used in comparative clinical PK and/or PD studies intended to support a 351(k) application?

A. I.10. (Proposed Answer): The requirements in 21 CFR 320.38 and 320.63 for retention of reserve samples of the products used in bioavailability and bioequivalence studies apply to applications submitted under section 505 of the FD&C Act. However, FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples in the same manner and for the same time period (at least 5
years) as described in 21 CFR 320.38 and 320.63 following a comparative clinical PK or PD study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected) that is intended to support a submission under section 351(k) of the PHS Act. Retention of samples used in a comparative clinical PK or PD study or other clinical study in which PK or PD samples are collected would serve the same purpose described in the Final Rule for the cited regulations (58 FR 25918, April 28, 1993). Specifically, reserve samples establish the identity of the products tested in the actual study, allow for confirmation of the validity and reliability of the results of the study, and facilitate investigation of further follow-up questions that arise after the studies are completed.

Q. I.11. Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?

A. I.11. (Proposed Answer): Yes. If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for the biosimilar product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.
Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- the mechanism(s) of action in each condition of use for which licensure is sought; this may include:
  - the target/receptor(s) for each relevant activity/function of the product;
  - the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
  - the relationships between product structure and target/receptor interactions;
  - the location and expression of the target/receptor(s);
- the PK and bio-distribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities); and
- any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Q. 1.12. How can an applicant demonstrate that its proposed injectable biosimilar product has the same “strength” as the reference product?

A. 1.12. (Proposed Answer): Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the “strength” of the proposed biosimilar product is the same as that of the reference product. As a scientific matter, there may be a need to take into account different factors and approaches in determining the “strength” of different types of biological products.

In general, we expect injectable biological products to have both the same total content of drug substance (in mass or units of activity in a container closure) and the same concentration of drug substance (in mass or units of activity per unit volume) as the reference product to have the same “strength” under section 351(k)(2)(A)(i)(IV) of the PHS Act. We note, however, that for certain complex biological products, a modified approach may be needed.

The total content of drug substance generally should be expressed using the same measure as the reference product. For example, if the strength of the reference product is expressed as milligrams (mg) per total volume in a container closure, for example mg/5 milliliters (mL), the proposed biosimilar product generally should also describe its strength in mg/5 mL, rather than units per 5 mL. If the total content of drug substance is expressed in units of activity (e.g., international units (IU) or units per total volume in a container closure), the units of the proposed biosimilar product should be the same as the reference product.
The concentration of the drug substance (in mass or units of activity per unit volume) generally should be expressed using the same measure as the reference product. The extinction coefficient used to calculate the concentration of a protein drug substance should be determined experimentally, and a justification for the experimental method should be provided. If the proposed biosimilar product is a dry solid (e.g., lyophilized) from which a constituted or reconstituted solution is prepared, then the 351(k) application should contain information demonstrating that the concentration of the proposed biosimilar product, when constituted or reconstituted, is the same as that of the reference product.

The requirement for a 351(k) application to contain information demonstrating that the proposed product and the reference product have the same “strength” applies to both biosimilar products and interchangeable products.

Q. I.13. What constitutes “publicly-available information” regarding FDA’s previous determination that the reference product is safe, pure, and potent to include in a 351(k) application?

A. I.13. (Proposed Answer): “Publicly-available information” in this context generally includes the types of information found in the “action package” for a BLA (see section 505(l)(2)(C) of the FD&C Act). However, FDA notes that submission of publicly available information composed of less than the action package for the reference product BLA will generally not be considered a bar to submission or approval of an acceptable 351(k) application.

FDA intends to post on the Agency’s Web site publicly available information regarding FDA’s previous determination that certain biological products are safe, pure, and potent in order to facilitate biosimilar development programs and submission of 351(k) applications. We note, however, that the publicly available information posted by FDA in this context does not necessarily include all of the information that would otherwise be disclosable in response to a Freedom of Information Act request.

Q. I.14. Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?

A. I.14. (Proposed Answer): Yes. Under the BPCI Act, FDA can make a determination of interchangeability in a 351(k) application or any supplement to a 351(k) application. An interchangeable product must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4) of the PHS Act. At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of
Q. I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?

A. I.15. (Proposed Answer): Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is required unless waived or deferred. An interchangeable product is not considered to have a “new active ingredient” for purposes of PREA. If a biological product is determined to be interchangeable with the reference product, a pediatric assessment of the interchangeable product is not required.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies during the investigational new drug (IND) stage of product development. See also the guidance for industry, How to Comply with the Pediatric Research Equity Act (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077855.pdf)

II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”

Q. II.1. How does FDA interpret the category of “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i)(1) of the PHS Act?

A. II.1. (Proposed Answer): The BPCI Act amends the definition of “biological product” in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized polypeptide)” and provides that an application for a biological product must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020, described in section 7002(c) of the Affordable Care Act.
FDA has developed the following regulatory definitions of “protein” and “chemically synthesized polypeptide” to implement the amended definition of “biological product” and provide clarity to prospective applicants regarding the statutory authority under which products will be regulated.

**Protein** — The term “protein” means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

Compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.

**Chemically synthesized polypeptide** — The term “chemically synthesized polypeptide” means any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.

A chemically synthesized polypeptide, as defined, is not a “biological product” and will be regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a “biological product.”

Chemically synthesized compounds greater than 99 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.

FDA’s interpretation of these statutory terms is informed by several factors, including the following. The scientific literature describes a “protein” as a defined sequence of alpha amino acid polymers linked by peptide bonds, and generally excludes “peptides” from the category of “protein.” A “peptide” generally refers to polymers that are smaller, perform fewer functions, contain less three-dimensional structure, are less likely to be post-translationally modified, and thus are generally characterized more easily than proteins.

Consistent with the scientific literature, FDA has decided that the term “protein” in the statutory definition of biological product does not include peptides. To enhance regulatory clarity and minimize administrative complexity, FDA has decided to distinguish proteins from peptides based solely on size (i.e., number of amino acids).

Although scientific references do not agree on the criteria that distinguish proteins from peptides, including the exact size at which a chain of amino acids becomes a protein, several references support a threshold of 40 amino acids as defining the upper size boundary of a peptide. Accordingly, FDA considers any polymer composed of 40 or fewer amino acids to be a peptide and not a protein. Therefore, unless a peptide otherwise meets the statutory definition of a
“biological product” (e.g., a peptide vaccine), it will be regulated as a drug under the FD&C Act.

The statutory category of “protein” parenthetically excludes “any chemically synthesized polypeptide.” There are several definitions of “polypeptide” in the scientific literature. Some are broad (e.g., polypeptide means any amino acid polymer), while others are more narrow (e.g., polypeptide means any amino acid polymer composed of fewer than 100 amino acids). FDA believes that a narrow definition of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the category of protein using a term that relates to a larger category of molecules. Therefore, FDA interprets the statutory exclusion for “chemically synthesized polypeptide” to mean any molecule that is made entirely by chemical synthesis and that is composed of up to 99 amino acids. Such molecules will be regulated as drugs under the FD&C Act, unless the chemically synthesized polypeptide otherwise meets the statutory definition of a “biological product.”

There may be additional considerations for proposed products that are combination products or meet the statutory definition of both a “device” and a “biological product.” We encourage prospective sponsors to contact FDA for further information on a product-specific basis.

Q. II.2. How is “product class” defined for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period?

A. II.2. (Proposed Answer): For purposes of section 7002(e)(2) of the Affordable Care Act, a proposed biological product will be considered to be in the same “product class” as a protein product previously approved under section 505 of the FD&C Act on or before March 23, 2010, if both products are homologous to the same gene-coded sequence (e.g., the INS gene for insulin and insulin glargine) with allowance for additional novel flanking sequences (including sequences from other genes). Products with discrete changes in gene-coded sequence or discrete changes in post-translational modifications may be in the same product class as the previously approved product even if the result may be a change in product pharmacokinetics.

For naturally derived protein products that do not have identified sequences linked to specific genes and that were approved under section 505 of the FD&C Act on or before March 23, 2010, a proposed biological product is in the same product class as the naturally derived protein product if both products share a primary biological activity (e.g., the 4-number Enzyme Commission code for enzyme activity).
However, for any protein product (whether naturally derived or otherwise), if the difference between the proposed product and the protein product previously approved under section 505 of the FD&C Act alters a biological target or effect, the products are not in the same product class for purposes of section 7002(e)(2) of the Affordable Care Act.

III. EXCLUSIVITY

Q. III.1. Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act?

A. III.1. (Proposed Answer): Yes. FDA is continuing to review the reference product exclusivity provisions of section 351(k)(7) of the PHS Act and has requested public comment on factors to consider in FDA’s interpretation of certain statutory provisions (see Docket No. FDA-2010-N-0477). An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant’s assertions regarding the eligibility of its proposed product for exclusivity. At this time, FDA suggests that an applicant’s request for reference product exclusivity specifically describe how the proposed product meets the statutory requirements in section 351(k)(7) of the PHS Act, and include adequate data and information to support the request.

Q. III.2. How can a prospective biosimilar applicant determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed?

A. III.2. (Proposed Answer): A searchable database for Orphan Designated and/or Approved Products and indications is available on FDA’s Web site, and is updated on a monthly basis (see http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm). FDA will not approve a subsequent application for the “same drug” for the same indication during the 7-year period of orphan exclusivity, except as otherwise provided in the FD&C Act and 21 CFR part 316.
EXHIBIT 2

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-7800
Email: ocod@fda.hhs.gov

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)

April 2015
Biosimilarity
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>3</td>
</tr>
<tr>
<td>QUESTIONS AND ANSWERS</td>
<td>5</td>
</tr>
<tr>
<td>I. BIOSIMILARITY OR INTERCHANGEABILITY</td>
<td>5</td>
</tr>
<tr>
<td>II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”</td>
<td>13</td>
</tr>
<tr>
<td>III. EXCLUSIVITY</td>
<td>16</td>
</tr>
</tbody>
</table>
Guidance for Industry

INTRODUCTION

This guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA’s interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The questions and answers (Q&As) are grouped below in the following categories:

- Biosimilarity or Interchangeability
- Provisions Related to Requirement to Submit a BLA for a “Biological Product”
- Exclusivity

The BPCI Act amends the Public Health Service Act (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)). On November 2 and 3, 2010, FDA held a public hearing and established a public docket to obtain input on specific issues and challenges associated with the implementation of the BPCI Act (see Docket No. FDA-2010-N-0477). This guidance describes FDA’s current interpretation of certain statutory requirements added by the BPCI Act and reflects consideration of the comments concerning those requirements that were submitted to the public docket.

1 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 and on the CBER guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER or CBER guidance page.
This guidance is one in a series of guidances that FDA is developing to implement the BPCI Act. The guidances address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants

When applicable, references to information in these guidances are included in this Q&A guidance.

The Q&A format is intended to promote transparency and facilitate development programs for proposed biosimilar products by addressing questions that may arise in the early stages of development. In addition, these Q&As respond to questions the Agency has received from prospective BLA and new drug application (NDA) applicants regarding the appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance to include additional Q&As as appropriate. Table 1 describes the status of the draft guidance Q&As that will be provided in Revision 1 to the draft guidance on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 and final guidance Q&As that are included in this guidance. FDA has maintained the original numbering of the Q&As used in the February 2012 draft guidance. Q&As that have not yet been finalized will appear in Revision 1 to the draft guidance, and the omission of these Q&As from the final guidance is marked by several asterisks between nonconsecutively numbered Q&As.

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2 The process by which FDA is requesting public comment on proposed Q&As and issuing new Q&As is described in the accompanying FEDERAL REGISTER notice.
Table 1. Status of Draft Guidance Q&As for Comment and Final Guidance Q&As

<table>
<thead>
<tr>
<th>Q&amp;A Category</th>
<th>Q&amp;A Numbers</th>
<th>Publication Date of Draft Guidance Q&amp;As for Comment</th>
<th>Comment Period</th>
<th>Publication Date of Final Guidance Q&amp;As</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part I. Biosimilarity or Interchangeability</td>
<td>I.1—I.8, I.11—I.12, I.15</td>
<td>2/15/12</td>
<td>2/15/12-4/16/12</td>
<td>April 2015</td>
</tr>
<tr>
<td></td>
<td>I.13—I.14</td>
<td>2/15/12</td>
<td>2/15/12-4/16/12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I.9—I.10 (revised)</td>
<td>(forthcoming)</td>
<td>(forthcoming)</td>
<td></td>
</tr>
<tr>
<td>Part II. Provisions Related To Requirement To Submit A BLA For A “Biological Product”</td>
<td>II.1—II.2</td>
<td>2/15/12</td>
<td>2/15/12-4/16/12</td>
<td>April 2015</td>
</tr>
<tr>
<td>Part III. Exclusivity</td>
<td>III.1 (revised)</td>
<td>(forthcoming)</td>
<td>(forthcoming)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>III.2</td>
<td>2/15/12</td>
<td>2/15/12-4/16/12</td>
<td>April 2015</td>
</tr>
</tbody>
</table>

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

BACKGROUND

The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (commonly referred to as the “Hatch-Waxman Act”), which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The implementation of an abbreviated licensure pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger and typically more complex structure of biological products, as well as the processes by which such products are manufactured. Most biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis.

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) defines biosimilarity to mean “that the biological product is highly similar to the reference product notwithstanding minor

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3 See section 505(b)(2) and 505(j) of the FD&C Act (21 U.S.C. 355(b)(2) and 355(j)).
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” (see section 351(i)(2) of the PHS Act). A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act). To meet the additional standard of “interchangeability,” an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

The BPCI Act also includes, among other provisions:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective (see section 351(k)(7) of the PHS Act);
- A 4-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted (see section 351(k)(7) of the PHS Act);
- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product (see section 351(k)(6) of the PHS Act);
- An exclusivity period for certain biological products for which pediatric studies are conducted in accordance with a written request (see section 351(m) of the PHS Act);
- A transition provision for biological products that have been or will be approved under section 505 of the FD&C Act (21 U.S.C. 355) before March 23, 2020 (see section 7002(e) of the Affordable Care Act); and
- A provision stating that a 351(k) application for a biosimilar product contains a “new active ingredient” for purposes of the Pediatric Research Equity Act (PREA) (see section 505B(n) of the FD&C Act).

The BPCI Act also establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act.
QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q. I.1. Whom should a sponsor contact with questions about its proposed biosimilar development program?

A. I.1. If the reference product for a proposed biosimilar product is regulated by the Center for Drug Evaluation and Research (CDER), contact the Therapeutic Biologics and Biosimilars Team (TBBT) in CDER’s Office of New Drugs at 301-796-0700.

If the reference product for a proposed biosimilar product is regulated by the Center for Biologics Evaluation and Research (CBER), contact the Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 240-402-7800 or by email to ocod@fda.hhs.gov.

For general questions related to FDA’s implementation of the BPCI Act, contact Sandra Benton in CDER’s Office of Medical Policy at 301-796-2500.

Q. I.2. When should a sponsor request a meeting with FDA to discuss their proposed biosimilar development program, and what data and information should a sponsor provide to FDA as background for this meeting?

A. I.2. Sponsors can request meetings at any time point in their development program. FDA recommends that sponsors refer to the draft guidance for industry titled Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants to determine the most appropriate meeting type to request. This draft guidance describes the different meeting types intended to facilitate biosimilar development programs in accordance with the Biosimilar User Fee Act of 2012 (BsUFA) and the criteria/data needed to support the request. The type of meeting granted will depend on the stage of product development and whether the information submitted in the meeting package meets the criteria for the type of meeting.

See FDA’s draft guidance for industry on Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

See FDA’s BsUFA website
http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm
Q. I.3. **Can a proposed biosimilar product have a different formulation than the reference product?**

A. I.3. Yes, differences between the formulation of a proposed product and the reference product may be acceptable. A 351(k) application must contain information demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. In addition, an applicant would need to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. It may be possible, for example, for a proposed product formulated without human serum albumin to demonstrate biosimilarity to a reference product formulated with human serum albumin. For more information about FDA’s current thinking on the interpretation of the statutory standard for biosimilarity, see FDA’s draft guidances for industry on *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* and *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.

Q. I.4. **Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product?**

A. I.4. Yes, some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled syringe or in an auto-injector device (which are considered the same dosage form), even if the reference product is licensed in a vial presentation, provided that the proposed product meets the statutory standard for biosimilarity and adequate performance data for the delivery device or container closure system are provided. For a proposed biosimilar product in a different delivery device or container closure system, the presentation must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

However, a prospective biosimilar applicant will not be able to obtain licensure under section 351(k) for its product when a design difference in the delivery device or container closure system results in any of the following:

- A clinically meaningful difference between the proposed product and the reference product in terms of safety, purity, and potency;
- A different route of administration or dosage form;
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved;

or otherwise does not meet the standard for biosimilarity.
Contains Nonbinding Recommendations

Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, FDA may consider whether the differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients, for patients to be safely alternated or switched between the reference product and one or more interchangeable products without the intervention of the prescribing healthcare provider. Additional performance data about the delivery device may also be necessary.

A proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

Q. I.5. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?

A. I.5. Yes, an applicant may obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed. An applicant must demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of safety, purity, and potency. In a limited number of circumstances, this may include providing information from one or more studies using a route of administration for which licensure is not requested (e.g., a study using subcutaneous administration may provide a more sensitive comparative assessment of immunogenicity of the reference product and a proposed biosimilar product, even though licensure of the proposed biosimilar product is requested only for the intravenous route of administration).

Q. I.6. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?

A. I.6. Yes, an applicant is not required to obtain licensure for all presentations for which the reference product is licensed. However, if an applicant seeks licensure for a particular indication or other condition of use for which the reference product is licensed and that indication or condition of use corresponds to a certain presentation of the reference product, the applicant may need to seek licensure for that particular presentation (see also questions and answers I.4 and I.5).

Q. I.7. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?
A. I.7. Yes, a biosimilar applicant generally may obtain licensure for fewer than all conditions of use for which the reference product is licensed. The 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).

Q. I.8. Can a sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?

A. I.8. Yes, a sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The acceptability of such approach will be evaluated on a case-by-case basis, and should be discussed in advance with the Agency. For certain complex biological products, a modified approach may be needed. A final determination about the adequacy of the scientific justification and bridge will be made during the review of the application.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- The relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;
Contains Nonbinding Recommendations

- The relationship between the license holder for the non-U.S.-licensed comparator product and BLA holder for the U.S.-licensed reference product;

- Whether the non-U.S.-licensed comparator product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries);

- Whether the non-U.S.-licensed comparator product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed; and

- The scientific bridge between the non-U.S.-licensed comparator product and the U.S.-licensed reference product, including comparative physicochemical characterization, biological assays/functional assays, degradation profiles under stressed conditions, and comparative clinical PK and, when appropriate, PD data, to address the impact of any differences in formulation or primary packaging on product performance.

A sponsor also should address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed comparator product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed comparator product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. The complexity of the products, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation) and the degree of heterogeneity associated with the product may impact the considerations for the scientific justification regarding the extent of bridging data. Additional factors that FDA may consider regarding the extent of bridging data include, but are not limited to, the following:

- Whether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same;
- The route of administration of the U.S.-licensed reference product and non-U.S.-licensed comparator products;
- The design of the physicochemical and biological/functional assessments and the use of multiple orthogonal methods with adequate sensitivity to detect differences among the products;
- The scientific justification for the selection of the non-U.S.-licensed comparator lots used to establish the scientific bridge and how the selected lots relate to the material used in the nonclinical and clinical studies. The scientific bridge should include a sufficient number of lots of non-U.S.-
licensed comparator product to adequately capture the variability in product quality attributes. When possible, the non-U.S.-licensed comparator lots used in the nonclinical or clinical studies should be included in the assessment performed to establish the analytical bridge.

Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.

* * * * *

Q. I.11. Can an applicant extrapolate clinical data intended to support a demonstration of biosimilarity in one condition of use to support licensure of the proposed biosimilar product in one or more additional conditions of use for which the reference product is licensed?

A. I.11. Yes. If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.
Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for which licensure is sought; this may include:
  - the target/receptor(s) for each relevant activity/function of the product;
  - the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptor(s);
  - the relationships between product structure and target/receptor interactions;
  - the location and expression of the target/receptor(s);
- The PK and bio-distribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities); and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity.

In choosing which condition of use to study that would permit subsequent extrapolation of clinical data to other conditions of use, FDA recommends that a sponsor consider choosing a condition of use that would be adequately sensitive to detect clinically meaningful differences between the two products.

The sponsor of a proposed product may obtain licensure only for a condition of use that has been previously licensed for the reference product. If a reference product has a condition of use that was licensed under section 506(c) of the FD&C Act and 21 CFR part 601, subpart E (accelerated approval), and the reference product’s clinical benefit in this condition of use has not yet been verified in postmarketing trials, the proposed product sponsor should consider studying another condition of use for which the reference product is licensed to avoid potential complications in the event that postmarketing trials fail to verify the clinical benefit of the reference product for the condition of use.

Q. I.12. How can an applicant demonstrate that its proposed injectable biosimilar product has the same “strength” as the reference product?
A. I.12. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the “strength” of the proposed biosimilar product is the same as that of the reference product. As a scientific matter, there may be a need to take into account different factors and approaches in determining the “strength” of different types of biological products.

In general, we expect injectable biological products to have both the same total content of drug substance (in mass or units of activity in a container closure) and the same concentration of drug substance (in mass or units of activity per unit volume) as the reference product to have the same “strength” under section 351(k)(2)(A)(i)(IV) of the PHS Act. We note, however, that for certain complex biological products, a modified approach may be needed.

The total content of drug substance generally should be expressed using the same measure as the reference product. For example, if the strength of the reference product is expressed as milligrams (mg) per total volume in a container closure, for example mg/5 milliliters (mL), the proposed biosimilar product generally should also describe its strength in mg/5 mL, rather than units per 5 mL. If the total content of drug substance is expressed in units of activity (e.g., international units (IU) or units per total volume in a container closure), the units of the proposed biosimilar product should be the same as the reference product.

The concentration of the drug substance (in mass or units of activity per unit volume) generally should be expressed using the same measure as the reference product. The extinction coefficient used to calculate the concentration of a protein drug substance should be determined experimentally, and a justification for the experimental method should be provided. If the proposed biosimilar product is a dry solid (e.g., lyophilized) from which a constituted or reconstituted solution is prepared, then the 351(k) application should contain information demonstrating that the concentration of the proposed biosimilar product, when constituted or reconstituted, is the same as that of the reference product.

The requirement for a 351(k) application to contain information demonstrating that the proposed product and the reference product have the same “strength” applies to both biosimilar products and interchangeable products.

* * * * *

Q. I.15. Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?

A. I.15. Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the
product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is required unless waived or deferred. Under the statute, an interchangeable product is not considered to have a “new active ingredient” for purposes of PREA. Therefore, if a biological product is determined to be interchangeable with the reference product, PREA would not be triggered and a pediatric assessment of the interchangeable product would not be required. However, if an applicant first seeks licensure of its proposed product as a non-interchangeable biosimilar product and intends to subsequently seek licensure of the product as interchangeable, the applicant still must address PREA requirements when it seeks initial licensure as a non-interchangeable biosimilar product.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies as early as practicable during product development. If there is no active IND for the proposed product and the sponsor intends to conduct a comparative clinical study as part of its development program, the initial pediatric study plan (PSP) should be submitted as a pre-IND submission. In this scenario, FDA encourages the sponsor to meet with FDA before submission of the initial PSP to discuss the details of the planned development program. It is expected that the sponsor will submit the initial PSP before initiating any comparative clinical study in its biosimilar development program. For more information see draft question and answer I.17 in FDA’s draft guidance for industry (revision 1) on Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, which, when finalized, will represent the Agency’s current thinking on this topic. See also the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf)

II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”

Q. II.1. How does FDA interpret the category of “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i)(1) of the PHS Act?

A. II.1. The BPCI Act amends the definition of “biological product” in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized
polypeptide)” and provides that an application for a biological product must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020, described in section 7002(e) of the Affordable Care Act.

FDA has developed the following regulatory definitions of “protein” and “chemically synthesized polypeptide” to implement the amended definition of “biological product” and provide clarity to prospective applicants regarding the statutory authority under which products will be regulated.

**Protein** — The term “protein” means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

For purposes of this definition, the size of the molecule is based on the total number of amino acids and is not limited to the number of amino acids in a contiguous sequence. However, compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.

**Chemically synthesized polypeptide** — The term “chemically synthesized polypeptide” means any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.

A chemically synthesized polypeptide, as defined, is not a “biological product” and will be regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a “biological product.”

For purposes of this definition, the size of the molecule is based on the total number of amino acids and is not limited to the number of amino acids in a contiguous sequence. However, chemically synthesized compounds greater than 99 amino acids in size will be scrutinized to determine whether they are related to a natural peptide of shorter length and, if so, whether the additional amino acids raise any concerns about the risk/benefit profile of the product.

FDA’s interpretation of these statutory terms is informed by several factors, including the following. The scientific literature describes a “protein” as a defined sequence of alpha amino acid polymers linked by peptide bonds, and generally excludes “peptides” from the category of “protein.” A “peptide” generally refers to polymers that are smaller, perform fewer functions, contain less three-dimensional structure, are less likely to be post-translationally modified, and thus are generally characterized more easily than proteins. Consistent with the scientific literature, FDA has decided that the term “protein” in the statutory definition of biological product does not include peptides. To enhance regulatory clarity and minimize administrative complexity, FDA has
decided to distinguish proteins from peptides based solely on size (i.e., number of amino acids).

In the absence of clear scientific consensus on the criteria that distinguish proteins from peptides, including the exact size at which a chain(s) of amino acids becomes a protein, FDA reviewed the pertinent literature and concluded that a threshold of 40 amino acids is appropriate for defining the upper size boundary of a peptide. Accordingly, FDA considers any polymer composed of 40 or fewer amino acids to be a peptide and not a protein. Therefore, unless a peptide otherwise meets the statutory definition of a “biological product” (e.g., a peptide vaccine), it will be regulated as a drug under the FD&C Act.

The statutory category of “protein” parenthetically excludes “any chemically synthesized polypeptide.” There are several definitions of “polypeptide” in the scientific literature. Some are broad (e.g., polypeptide means any amino acid polymer), while others are more narrow (e.g., polypeptide means any amino acid polymer composed of fewer than 100 amino acids). FDA believes that a narrow definition of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the category of protein using a term that relates to a larger category of molecules. Therefore, FDA interprets the statutory exclusion for “chemically synthesized polypeptide” to mean any molecule that is made entirely by chemical synthesis and that is composed of up to 99 amino acids. Such molecules will be regulated as drugs under the FD&C Act, unless the chemically synthesized polypeptide otherwise meets the statutory definition of a “biological product.”

There may be additional considerations for proposed products that are combination products or meet the statutory definition of both a “device” and a “biological product.” We encourage prospective sponsors to contact FDA for further information on a product-specific basis.

Q. II.2. How is “product class” defined for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period?

A. II.2. For purposes of section 7002(e)(2) of the Affordable Care Act, a proposed biological product will be considered to be in the same “product class” as a protein product previously approved under section 505 of the FD&C Act on or before March 23, 2010, if both products are homologous to the same gene-coded sequence (e.g., the INS gene for insulin and insulin glargine) with allowance for additional novel flanking sequences (including sequences from other genes). Products with discrete changes in gene-coded sequence or discrete changes in post-translational modifications may be in the same product class as the previously approved product even if the result may be a change in product pharmacokinetics.
For naturally derived protein products that do not have identified sequences linked to specific genes and that were approved under section 505 of the FD&C Act on or before March 23, 2010, a proposed biological product is in the same product class as the naturally derived protein product if both products share a primary biological activity (e.g., the 4-number Enzyme Commission code for enzyme activity).

However, for any protein product (whether naturally derived or otherwise), if the difference between the proposed product and the protein product previously approved under section 505 of the FD&C Act alters a biological target or effect, the products are not in the same product class for purposes of section 7002(e)(2) of the Affordable Care Act.

### III. EXCLUSIVITY

**Q. III.2. How can a prospective biosimilar applicant determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed?**

**A. III.2.** A searchable database for Orphan Designated and/or Approved Products and indications is available on FDA’s Web site, and is updated on a monthly basis (see http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm). FDA will not approve a subsequent application for the “same drug” for the same indication during the 7-year period of orphan exclusivity, except as otherwise provided in the FD&C Act and 21 CFR part 316.
EXHIBIT 3
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Sandra Benton at 301-796-1042 or (CBER) Office of Communication, Outreach and Development at 1-800-835-4709 or 240-402-8010.
New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Biosimilars
Revision 2
TABLE OF CONTENTS

INTRODUCTION......................................................................................................................... 1
BACKGROUND ........................................................................................................................... 3
QUESTIONS AND ANSWERS................................................................................................... 5
   I. BIOSIMILARITY OR INTERCHANGEABILITY........................................................... 5
   II. PROVISIONS RELATED TO REQUIREMENTS TO SUBMIT A BLA FOR A
       “BIOLOGICAL PRODUCT”.................................................................................... 12
   III. EXCLUSIVITY ........................................................................................................ 14
New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

INTRODUCTION

This draft guidance document provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of proposed biosimilars and interchangeable biosimilars, as well as to describe FDA’s interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act amended the Public Health Service Act (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) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA’s interpretation of the BPCI Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q&As respond to questions the Agency has received from prospective applicants regarding

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

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

2 In this draft guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) biosimilar or biosimilar product refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) interchangeable biosimilar or interchangeable product refers to a biosimilar product that FDA has also determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act). Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this draft guidance.
the appropriate statutory authority under which certain products will be regulated. FDA intends
to update this draft guidance document to include additional Q&As as appropriate.

This draft guidance document revises the draft guidance document, Biosimilars: Additional
Questions and Answers Regarding Implementation of the Biologics Price Competition and
Innovation Act of 2009. The draft guidance document contains Q&As distributed for comment
purposes only and includes new Q&As, as well as revisions to Q&As that appeared in previous
versions of the draft or final guidance documents. Additional information about the Q&A format
for this draft guidance document is provided in the Background section.

FDA is also issuing a final guidance document entitled Questions and Answers on Biosimilar
Development and the BPCI Act. This final guidance document is part of a series of guidance
documents that FDA has developed to facilitate development of biosimilar and interchangeable
products. The final guidance documents issued to date address a broad range of issues,
including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein
  Product to a Reference Product (April 2015)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  (April 2015)
- Questions and Answers on Biosimilar Development and the BPCI Act (December 2018)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a
  Reference Product (December 2016)
- Labeling for Biosimilar Products (July 2018)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when
finalized, will represent FDA’s current thinking. These draft guidance documents include:

- Considerations in Demonstrating Interchangeability With a Reference Product
  (January 2017)
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA
  Products (June 2018)
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a)
  of the PHS Act (August 2014)

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3 FDA has adjusted the title of this draft guidance to more clearly communicate that this draft guidance contains draft questions and answers.
In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

**BACKGROUND**

The **BPCI Act**

The BPCI Act was enacted as part of the ACA on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar or interchangeable product.

Section 351(i) defines the term **biosimilar** or **biosimilarity** “in reference to a biological product that is the subject of an application under [section 351(k)]” to mean “that the biological product is highly similar to the reference product\(^4\) 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” (see section 351(i)(2) of the PHS Act).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product “is biosimilar to the reference product” and “can be expected to produce the same clinical result as the reference product in any given patient”\(^5\) and that “for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”\(^6\)

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\(^4\) *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 (section 351(i)(4) of the PHS Act).

\(^5\) Section 351(k)(4)(A) of the PHS Act.

\(^6\) Section 351(k)(4)(B) of the PHS Act.
Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that “the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

In this draft guidance document, the terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe products that are under development or are the subject of a pending 351(k) biologics license application (BLA).

Certain other provisions of the BPCI Act are discussed in the context of the relevant Q&A.

“Question and Answer” Guidance Format

This draft guidance document is a companion to the final guidance document, *Questions and Answers on Biosimilar Development and the BPCI Act*. In this pair of guidance documents, FDA issues each Q&A in draft form in this draft guidance document, receives comments on the draft Q&A, and, as appropriate, moves the Q&A to the final guidance document, after reviewing comments and incorporating suggested changes to the Q&A, when appropriate. A Q&A that was previously in the final guidance document may be withdrawn and moved to the draft guidance document if FDA determines that the Q&A should be revised in some respect and reissued in a revised draft Q&A for comment. A Q&A also may be withdrawn and removed from the Q&A guidance documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

A reference will follow each question in this draft guidance document describing the publication date of the current version of the Q&A, and whether the Q&A has been added to or modified in this draft guidance document. FDA has maintained the original numbering of the guidance Q&As used in the April 2015 final guidance document (*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*) and May 2015 draft guidance document (*Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). For ease of reference, a Q&A retains the same number when it moves from the draft guidance document to the final guidance document and, where appropriate, when a Q&A is withdrawn from the final guidance document and moved to the draft guidance document.

Where a Q&A has been withdrawn from the final guidance document, this is marked in the final guidance document by several asterisks between nonconsecutively numbered Q&As and, where appropriate, explanatory text.
QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

* * * * *

Q. I.12. How can an applicant demonstrate that its proposed injectable biosimilar product or proposed injectable interchangeable product has the same “strength” as the reference product?

[Moved to Draft from Final December 2018]

A. I.12. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the “strength” of the proposed biosimilar product or proposed interchangeable product is the same as that of the reference product. Data and information generated as part of the analytical similarity assessment may inform the determination that a proposed biosimilar product or proposed interchangeable product has the same strength as its reference product. As a scientific matter, there may be a need to take into account different factors and approaches in determining the “strength” of different biological products. Sponsors should discuss their proposed approach with FDA and provide an adequate scientific basis for their approach to demonstrating same strength.

In general, a sponsor of a proposed biosimilar product or proposed interchangeable product with an “injection” dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) and the same concentration of drug substance (in mass or units of activity per unit volume). In general, for a proposed biosimilar product or proposed interchangeable product that is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, a sponsor can demonstrate that the product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity).

Although not a part of demonstrating same “strength,” if the proposed biosimilar product or proposed interchangeable product is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, the 351(k) application generally should contain information that the concentration of the proposed biosimilar product or proposed interchangeable product, when constituted or reconstituted, is the same as that of the reference product, when constituted or reconstituted.

A sponsor should determine the content of drug substance for both the reference product and the proposed biosimilar product or proposed interchangeable product.
using the same method. The strength of the proposed product generally should be expressed using the same units of measure as the reference product.

Q. I.16. How can a proposed biosimilar product applicant fulfill the requirement for pediatric assessments or investigations under the Pediatric Research Equity Act (PREA)?
[Updated/Retained in Draft December 2018]

A. I.16. Applicants for proposed biosimilar products should address PREA requirements based upon the nature and extent of pediatric information in the reference product labeling. PREA requirements are applicable to proposed biosimilar products that have not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product; or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

As a preliminary matter, we note that there are differences in the use of the term “extrapolation” in the context of a proposed biosimilar product under the PHS Act and in the context of PREA.

- An applicant may provide scientific justification for “extrapolation” to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use. For more information on extrapolation in this context, see FDA’s guidance for industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

- “Pediatric extrapolation” refers to establishing the effectiveness of a drug in a pediatric population without requiring a separate study in that population when the course of the disease and the effects of the drug are sufficiently similar in the pediatric population and the adult population (or another pediatric population) in which the drug has been studied and shown to be effective (see section 505B(a)(2)(B) and (a)(3)(B) of the Federal Food Drug and Cosmetic Act (FD&C Act).

In the discussion that follows, the term “extrapolation” generally will be used to refer to extrapolation to support approval of a biosimilar product under section 351(k) of the PHS Act for one or more conditions of use, and not to pediatric extrapolation.

- Adequate pediatric information in reference product labeling

If the labeling for the reference product contains adequate pediatric information (e.g., information reflecting an adequate pediatric assessment)
with respect to an indication for which a biosimilar applicant seeks licensure in adults, the biosimilar applicant may fulfill PREA requirements for that indication by satisfying the statutory requirements for showing biosimilarity and providing an adequate scientific justification under the BPCI Act for extrapolating the pediatric information from the reference product to the proposed biosimilar product.

If the submitted scientific justification for extrapolation under section 351(k) of the PHS Act is inadequate, a biosimilar applicant must submit appropriate data to fulfill applicable PREA requirements.

- Lack of adequate pediatric information in reference product labeling

If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and applicable PREA requirements were deferred for the reference product for those pediatric age groups, a biosimilar applicant should request a deferral of PREA requirements for those pediatric age groups. The biosimilar applicant should amend or supplement its 351(k) BLA, as appropriate, to seek approval for updated labeling, supported by biosimilar extrapolation or appropriate data, that includes relevant pediatric information after the reference product labeling is updated with that information.

If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and PREA requirements were waived for, or inapplicable to, the reference product for those pediatric age groups, a biosimilar applicant should note this information in its initial pediatric study plan (iPSP), if any, but does not need to request a waiver of PREA requirements for those age groups.

For proposed biosimilars, obligations under PREA are circumscribed by the BPCI Act to require an assessment only for indications and age groups or other conditions of use in which the reference product has been or will be assessed. In other words, the Agency has determined that PREA requirements are applicable to a proposed biosimilar product that has not been determined to be interchangeable with a reference product only to the extent that compliance with PREA would not result in: (1) a condition of use that has not been previously approved for the reference product, or (2) a dosage form, strength, or route of administration that differs from that of the reference product.

FDA’s recommendations to biosimilar applicants with respect to the PREA requirements reflect a clarification based on the Agency’s interpretation of the
interaction between section 505B of the FD&C Act (PREA) and section 351(k) of the PHS Act. Biosimilar applicants previously requested, and the Agency granted, waivers in instances where PREA requirements were waived for or determined to be inapplicable to the reference product. However, upon further consideration, waivers for biosimilars applicants under those circumstances were not necessary, and the practice is more accurately described in terms of the Agency’s interpretation of the BPCI Act and PREA. The BPCI Act added section 351(k) of the PHS Act and amended section 505B of the FD&C Act to specify that PREA is applicable to a biosimilar product that has not been determined to be interchangeable with a reference product (see section 7002(a), (d)(2) of the BPCI Act). FDA reads section 351(k) of the PHS Act and PREA together with respect to the need to conduct assessments of and seek licensure for certain pediatric uses and pediatric formulations. An application submitted under section 351(k) of the PHS Act must include, among other things, information demonstrating that “the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product” and “the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product” (section 351(k)(2)(A)(i)(III)-(IV) of the PHS Act). FDA has determined that, when the reference product does not have adequate pediatric use information in its labeling or an age-appropriate formulation for a relevant pediatric population, the obligations for the biosimilar applicant under PREA are circumscribed by section 351(k) of the PHS Act insofar as the biosimilar applicant would not be expected to obtain licensure for a pediatric use (or describe that use in product labeling) that has not been licensed for the reference product and would not be expected to obtain licensure of a product that would result in a dosage form, strength, or route of administration that differs from that of the reference product.

By establishing an abbreviated licensure pathway for biosimilar and interchangeable products, the BPCI Act reflects the strong public health interest in the licensure and availability of those products. Such licensure could result in increased competition, as well as greater access to biological products. The Agency’s interpretation of section 351(k) and PREA assures that biosimilar applicants are not subject to greater regulatory burdens than those faced by reference product sponsors with respect to the study of pediatric uses.

This approach preserves the intent and availability of an abbreviated licensure pathway for biosimilars, while helping to ensure that a biosimilar product is labeled and formulated for relevant pediatric conditions of use that have been approved for the reference product. FDA also recognizes the important interests furthered by PREA and appreciates the need to study pediatric uses of biological products and to include pediatric use information in product labeling. Consequently, in appropriate cases, FDA may take additional steps within its authority to assure that pediatric use information is included in biological product labeling.
labeling.\footnote{For instance, if the Agency determines that the basis for the reference product’s waiver under PREA no longer applies to a particular age group (e.g., because it is now feasible to study a younger pediatric age group), FDA may, as appropriate, contact the 351(k) biosimilar product sponsor, as well as the reference product sponsor, and require further action by both parties to comply with PREA. \textit{See § 505B(a)(5) of the FD&C Act.}} Such actions may include invoking the “marketed drugs” provision under PREA, in certain circumstances, to require sponsors to conduct pediatric assessments, or take other appropriate steps, to support pediatric labeling for both the biosimilar product and the reference product.\footnote{\textit{See § 505B(b) of the FD&C Act.}}

If a biosimilar applicant believes that none of the situations described above applies to its proposed product, the applicant should contact FDA for further information.

\textbf{Q. I.20. What is the nature and type of information that a sponsor should provide to support a post-approval manufacturing change for a licensed biosimilar product?}

\textbf{[New December 2018]}

\textbf{A. I.20} In general, a sponsor who intends to make a manufacturing change to a licensed biosimilar product should follow the principles outlined in the International Council for Harmonisation (ICH) guidance for industry \textit{Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (June 2005)}. Accordingly, the sponsor should provide sufficient data and information to demonstrate the comparability of the biosimilar product before and after the manufacturing change. The comparability assessment should include: a) side-by-side analytical comparison of a sufficient number of lots of pre-change and post-change material, including an assessment of stability; and b) a comparison of analytical data from the post-change material to historical analytical data from lots used in the analytical similarity assessment, including data from lots used in clinical studies that supported licensure of the biosimilar product. A well-qualified, in-house reference standard should also be included in the comparability exercise. In certain cases, additional reference materials may be included in the comparability study. The extent of data and information necessary to establish comparability would be commensurate with the type of manufacturing change and its potential impact on product quality, safety, and efficacy.

In addition, FDA continues to consider the nature and type of information a sponsor should provide to support a post-approval manufacturing change to a biological product determined by FDA to be interchangeable with the reference product under section 351(k)(4) of the PHS Act. FDA intends to provide specific recommendations for post-approval manufacturing changes to interchangeable biological products in future guidance.
A sponsor may seek approval, in a supplement to an approved 351(k) BLA, of a route of administration, a dosage form, or a strength that is the same as that of the reference product, but that has not previously been licensed under the 351(k) BLA. FDA intends to provide specific recommendations on this topic in future guidance.

Q. I.21. **May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) application, of a route of administration, a dosage form, or a strength that is not the same as that of the reference product?**  
[New December 2018]

A. I.21. No. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, a 351(k) application must include information demonstrating that “the route of administration, the dosage form, and the strength” of the proposed biosimilar or interchangeable product “are the same as those of the reference product.” An applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a route of administration, a dosage form, or a strength that is not the same as that of the reference product.

Q. I.22. **May a sponsor seek approval, in a 351(k) application or a supplement to an approved 351(k) application, for a condition of use that has not previously been approved for the reference product?**  
[New December 2018]

A. I.22 No. Under section 351(k)(2)(A)(i)(III) of the PHS Act, the 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the proposed biosimilar or interchangeable product have been previously approved for the reference product. A 351(k) applicant may not seek approval, in a 351(k) application or a supplement to an approved 351(k) application, of a condition of use (e.g., indication, dosing regimen) that has not been previously approved for the reference product.

Q.I.23 **May a prospective 351(k) BLA applicant request a letter from FDA stating that study protocols intended to support a 351(k) application contain safety protections comparable to an applicable Risk Evaluation and Mitigation Strategy (REMS) for the reference product?**  
[New December 2018]

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As described elsewhere in this draft guidance (Q&A I.21), a 351(k) applicant may not seek approval of a route of administration, a dosage form, or a strength that is not the same as the reference product, including in a supplement to an approved 351(k) application. This draft guidance, when finalized, will represent FDA’s current thinking on this topic. See Q&A I.21 for additional information.
A.I.23 Yes. There have been reports of instances in which a reference product holder has refused to sell product to a prospective applicant for a competing product that is seeking to conduct studies to support approval, and the reference product holder cites the risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) for the reference product as justification.

In the interest of facilitating a prospective biosimilar applicant’s access to supplies of the reference product to conduct the testing necessary to support 351(k) BLA approval, FDA will, on request, review (one or more) study protocols submitted by a prospective 351(k) BLA applicant to assess whether they provide safety protections comparable to those in the applicable REMS with ETASU. If the Agency determines that comparable protections exist, FDA will notify the prospective 351(k) BLA applicant. If requested to do so by the prospective 351(k) BLA applicant, FDA will then issue a separate letter to the reference product holder stating that comparable protections exist and indicating that FDA will not consider it to be a violation of the REMS for the reference product holder to provide the prospective 351(k) BLA applicant with a sufficient quantity of the reference product to allow it to perform testing necessary to support its 351(k) BLA.

Requesting such a protocol review or letter is not a legal requirement. If a prospective 351(k) BLA applicant wishes to request such a letter or protocol review, however, it should (1) confirm that the product at issue is subject to a REMS with ETASU by checking the Agency’s online listing of approved REMS\(^\text{10}\), and (2) contact FDA for more information. For contact information, see FDA’s website, “Biosimilars,” available at \url{https://www.fda.gov/biosimilars} and click on the link, “Industry Information and Guidance” listed in the left column.

Q.I.24 May an applicant submit data and information to support approval of a proposed biosimilar or interchangeable product for an indication for which the reference product has unexpired orphan exclusivity?

[New December 2018]

A.I.24 Yes. An applicant may submit data and information to support approval of a proposed biosimilar or interchangeable product for one or more indications for which the reference product has unexpired orphan exclusivity. For example, an applicant may submit data and information intended to provide sufficient scientific justification for extrapolation to support approval of a proposed biosimilar or interchangeable product for one or more indications for which the reference product has unexpired orphan exclusivity. However, FDA will not be able to approve the proposed biosimilar or interchangeable product for the protected indication(s) until the orphan exclusivity expires.

\(^{10}\) See Approved Risk Evaluation and Mitigation Strategies (REMS): \url{https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm}
II. PROVISIONS RELATED TO REQUIREMENTS TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”

Q. II.1. How does FDA interpret the category of “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i)(1) of the PHS Act? [Moved to Draft from Final December 2018]

A. II.1. The BPCI Act amends the definition of “biological product” in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized polypeptide)” and provides that an application for a biological product must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020, described in section 7002(e) of the Affordable Care Act.

FDA has developed the following interpretations of the statutory terms “protein” and “chemically synthesized polypeptide” to implement the amended definition of “biological product” and provide clarity to prospective applicants regarding the statutory authority under which such products are regulated.

Protein — FDA interprets the term “protein” to mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

Where a single amino acid polymer is greater than 40 amino acids in size and is related to a naturally occurring polypeptide, such polymer would be reviewed to determine whether the additional amino acids that cause the peptide to exceed 40 amino acids in size raise any concerns about the risk/benefit profile of the product.

Some amino acid polymers are composed of multiple amino acid chains that are associated with each other. When two or more amino acid chains are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of our interpretation of the statutory terms “protein” and “chemically synthesized polypeptide” is based on the total number of amino acids in those chains, and is not limited to the number of amino acids in a contiguous sequence. In other words, the amino acids in each such amino acid chain will be added together to determine whether the product meets the numerical threshold in FDA’s interpretation of the terms “protein” and “chemically synthesized polypeptide.” However, for products with amino acid chains that are associated with each other in a manner that is not found in nature (i.e., amino acid chains that...
are associated with each other in a novel manner that is not found in naturally
occurring proteins), FDA intends to conduct a fact-specific, case-by-case analysis
to determine whether the size of the amino acid polymer, for purposes of our
interpretation of the statutory terms “protein” and “chemically synthesized
polypeptide,” should be based on adding each of the amino acids in the amino
acid chains together or should be based on separate consideration of the amino
acid chains (e.g., the number of amino acids in the largest chain). In such cases,
FDA may consider in its analysis, among other things, any structural or functional
characteristics of the product.

Chemically synthesized polypeptide — The term “chemically synthesized
polypeptide” means any alpha amino acid polymer that (1) is made entirely by
chemical synthesis; and (2) is greater than 40 amino acids but less than 100 amino
acids in size.

A chemically synthesized polypeptide, as described, is not a “biological product”
and will be regulated as a drug under the FD&C Act unless the polypeptide
otherwise meets the statutory definition of a “biological product.”

Where a single amino acid polymer is greater than 99 amino acids in size and is
related to a naturally occurring peptide or polypeptide of shorter length, such
polymer would be reviewed to determine whether the additional amino acids that
cause the polymer to exceed 99 amino acids in size raise any concerns about the
risk/benefit profile of the product.

FDA’s interpretation of these statutory terms is informed by several factors. The
scientific literature describes a “protein” as a defined sequence of alpha amino
acid polymers linked by peptide bonds, and generally excludes “peptides” from
the category of “protein.” A “peptide” generally refers to polymers that are
smaller, perform fewer functions, contain less three-dimensional structure, are
less likely to be post-translationally modified, and thus are generally characterized
more easily than proteins. Consistent with the scientific literature, FDA interprets
the term “protein” in the statutory definition of biological product in a manner
that does not include peptides. To enhance regulatory clarity and minimize
administrative complexity, FDA has decided to distinguish proteins from peptides
based solely on size (i.e., number of amino acids).

In the absence of clear scientific consensus on the criteria that distinguish proteins
from peptides, including the exact size at which a chain(s) of amino acids
becomes a protein, FDA reviewed the pertinent literature and concluded that a
threshold of 40 amino acids is appropriate for defining the upper size boundary of
a peptide. Accordingly, FDA interprets the BPCI Act such that any polymer
composed of 40 or fewer amino acids is a peptide and not a protein. Therefore,
unless a peptide otherwise meets the statutory definition of a “biological product” (e.g., a peptide vaccine), it will be regulated as a drug under the FD&C Act.

The statutory category of “protein” parenthetically excludes “any chemically synthesized polypeptide.” There are several definitions of “polypeptide” in the scientific literature. Some are broad (e.g., polypeptide means any amino acid polymer), while others are more narrow (e.g., polypeptide means any amino acid polymer composed of fewer than 100 amino acids). FDA believes that a narrow interpretation of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the category of “protein” that includes a broader category of molecules. Therefore, FDA interprets the statutory exclusion for “chemically synthesized polypeptide” to mean any molecule that is made entirely by chemical synthesis and that is composed of greater than 40 amino acids but less than 100 amino acids in size. Such molecules will be regulated as drugs under the FD&C Act, unless the chemically synthesized polypeptide otherwise meets the statutory definition of a “biological product.”

There may be additional considerations for proposed products that are combination products or meet the statutory definition of both a “device” and a “biological product.” We encourage prospective sponsors to contact FDA for further information on a product-specific basis.

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III. EXCLUSIVITY

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EXHIBIT 4
APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

29th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2009
The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2008.

29th EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2009
under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

AN Solutions and powders for aerosolization

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded AN. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded BN, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded AN if the bioequivalence standard is based upon in vitro methodology, if bioequivalence needs to be demonstrated by in vivo methodology then the drug products will be coded AB.

AO Injectable oil solutions

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included on the List (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.
The strength of parenteral drugs products is defined as the total drug content of the container. Until recently the strength of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.

With the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug, it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end the OGD has started to display the strength of all new approvals of parenteral solutions. Previously we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/ml. If this drug product had a 20 ml and 60 ml container approved the two products would be shown as 1Gm / 20ml (50mg/ml) and 3Gm / 60ml (50mg/ml).

AT Topical products

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of in vivo bioequivalence has been granted and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded AT. Pharmaceutically equivalent topical products that raise questions of bioequivalence, including all post-1962 non-solution topical drug products, are coded AB when supported by adequate bioequivalence data, and BT in the absence of such data.

"B" CODES

Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

"B" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients. Drug products designated with a "B" code fall under one of three main policies:

(1) the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bio-equivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or

(2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

(3) the drug products are under regulatory review.

The specific coding definitions and policies for the "B" sub-codes are as follows:
APPROVED DRUG PRODUCTS
WITH THERAPEUTIC EQUIVALENCE EVALUATIONS
23rd EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2003
APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2001.

23RD EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2003
bioequivalent to Adalat® CC would be assigned a rating of AB1 and those bioequivalent to Procardia XL® would be assigned a rating of AB2. (The assignment of an AB1 or AB2 rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated either with an AB or three-character code or is single source in the List. Drugs coded as AB under a heading are considered therapeutically equivalent only to other drugs coded as AB under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

**AN Solutions and powders for aerosolization**

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded AN. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded BN, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded AN if the bioequivalence standard is based upon in vitro methodology, if bioequivalence needs to be demonstrated by in vivo methodology then the drug products will be coded AB.

**AO Injectable oil solutions**

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

**AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions**

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are all considered to be pharmaceutically and therapeutically equivalent provided they are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included on the List (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in
plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

The strength of parenteral drugs products is defined as the total drug content of the container. Until recently the strength of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.

With the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end the OGD has started to display the strength of all new approvals of parenteral solutions. Previously we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/ml. If this drug product had a 20 ml and 60 ml container approved the two products would be shown as 1Gm / 20ml (50mg/ml) and 3Gm / 60ml (50mg/ml).

**AT Topical products**

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2. the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

3. the drug products are under regulatory review.

xvii
APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

35th EDITION

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MEDICAL PRODUCTS AND TOBACCO
OFFICE OF GENERIC DRUGS

2015
The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2014.

35th EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF MEDICAL PRODUCTS AND TOBACCO
OFFICE OF GENERIC DRUGS

2015
coded BN, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded AN if the bioequivalence standard is based upon in vitro methodology, if bioequivalence needs to be demonstrated by in vivo methodology then the drug products will be coded AB.

**AO Injectable oil solutions**

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**AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions**

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included on the List (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

The strength of parenteral drugs products is defined as the total drug content of the container. Until recently the strength of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.
With the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug, it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end the OGD has started to display the strength of all new approvals of parenteral solutions. Previously we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/ml. If this drug product had a 20ml and 60ml container approved the two products would be shown as 1Gm / 20ml (50mg/ml) and 3Gm / 60ml (50mg/ml).

**AT  Topical products**

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of in vivo bioequivalence has been granted and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded **AT**. Pharmaceutically equivalent topical products that raise questions of bioequivalence, including all post-1962 non-solution topical drug products, are coded **AB** when supported by adequate bioequivalence data, and **BT** in the absence of such data.

"**B**" CODES

Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

"**B**" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients. Drug products designated with a "**B**" code fall under one of three main policies:

1. the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bio-equivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or

2. the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

3. the drug products are under regulatory review.

The specific coding definitions and policies for the "**B**" sub-codes are as follows:
EXHIBIT 7
FDA Drug Safety Communication: Important change to heparin container labels to clearly state the total drug strength

Safety Announcement
Additional Information for Patients and Caregivers
Additional Information for Health Care Professionals, Hospitals, and Pharmacies
Additional Background Information

Safety Announcement

[12-06-2012] The U.S. Food and Drug Administration (FDA) is notifying health care professionals, caregivers, and patients about a change to the container and carton labels for heparin products, which are blood-thinning agents that prevent the formation of blood clots.

This label change will require manufacturers of Heparin Lock Flush Solution, USP and Heparin Sodium Injection, USP to clearly state the strength of the entire container of the medication followed by how much of the medication is in 1 milliliter (mL). These modifications will eliminate the need for health care professionals to calculate the total amount of heparin medication in a product containing more than 1 mL, thereby reducing the risk of miscalculations that may result in medication errors.

Facts about heparin

- A blood thinner that works by decreasing the clotting ability of the blood
- Used to prevent blood clots from forming in people who have certain medical conditions or who are undergoing certain medical procedures that may increase the chance that clots will form
- Used to stop the growth of clots that have already formed in the blood vessels and to prevent blood clots from forming in catheters that are left in veins over a period of time

FDA supports the United States Pharmacopeia (USP)* proposal to revise the labeling section of USP monographs for Heparin Lock Flush Solution, USP and Heparin Sodium Injection, USP to clearly state the total drug strength on the label. This will ensure that labels for heparin products comply with USP’s general requirements for all small-volume injectable products, which currently display the total drug content.

Health care professionals, caregivers, and patients should be aware that there will be a transition period before and after the official implementation date on May 1, 2013, during which both the current heparin container labels and the revised heparin container labels will be available in the marketplace. To minimize the potential for medication errors, users should consider separating the supplies of “current” and “revised” labeled heparin, and use all of the supplies of the “current” heparin before using products with the “revised” container label.

*USP is a scientific nonprofit organization that develops standards for the identity, strength, quality, and purity of drugs and drug ingredients marketed in the U.S. These standards are published in USP’s official compendia, U.S. Pharmacopeia and National Formulary.

Current and Revised Heparin Labels
The proposed revision to the labeling sections in the heparin monographs will require the labels to comply with the USP standards for injectable medications, specifically USP 35-NF 30 General Chapter <1> Injections section.

The following formats are those FDA considers acceptable for heparin vials and syringes that contain more than 1 mL:

> *The strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses.*

**Example 1:**

50,000 USP units per 10 mL  
(5,000 USP units per mL)

**Example 2:**

50,000 USP units/10 mL  
(5,000 USP units/mL)

The following format is acceptable for contents of less than 1 mL:
The strength per fraction of a mL should be the only expression of strength.

100 USP units/0.5 mL

Strength per single mL should be expressed as mg/mL, not mg/1 mL.

5,000 USP units/mL

Additional Information for Patients and Caregivers

- Always ask your health care professional to look at the label on the heparin container and to check the dose and volume to be administered.
- Contact your health care professional if you have any questions or concerns about heparin.
- Report medication errors or side effects from the use of heparin to FDA’s MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals, Hospitals, and Pharmacies

- To minimize the potential for medication errors, hospitals and pharmacies may wish to consider separating the supplies of “current” and “revised” labeled heparin and exhausting the supplies of the “current” heparin before transitioning to products with the “revised” label.
- Always look at the label on the heparin vial being dispensed and counsel the patient or caregiver on how to administer the correct dose.
- Report medication errors or adverse events involving heparin to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Background Information

In 2003, the United States Pharmacopeia’s (USP) Safe Medication Use Expert Committee became aware of medication errors involving the expression of strength in the labeling for all injectable products. Containers labeled with the strength per mL were often misunderstood as the total drug content, which could result in dosing errors with serious consequences to patients. To address this safety issue, the USP Parenteral Products—Industrial Expert Committee approved the new “Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products” section of the USP General Chapter <1> Injections in 2007, and the text became official on February 1, 2009. General Chapter <1> requires that the strength per total volume should be the primary and prominent expression of strength on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. Container labels that have already been changed to state the strength per total volume have had no reported medication errors.
Since 2009, concerns have arisen about the conflict in labeling requirements between the Heparin Sodium Injection and Heparin Lock Flush Solution monographs and the General Chapter <1> Injections section on “Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.” The labeling requirement in the current heparin monographs states that the label must reflect only strength per mL, except it also allows for single-dose vials to be labeled additionally to indicate the total drug content. To address this conflict, USP has proposed revising the labeling section of the heparin monographs to ensure that the heparin container labels comply with the USP General Chapter <1> Injections section.

The proposed revision to the labeling sections in the heparin monographs will require the container labels to comply with the USP 35-NF 30 General Chapter <1> Injections section that reads in part:

"[T]he strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL."

The official implementation date for the USP Heparin Lock Flush Solution and USP Heparin Sodium Injection monographs is May 1, 2013. Manufacturers are expected to have revised their heparin labels accordingly by that time. A transition period will occur during which both the current heparin container labels and the revised heparin container labels will appear in the marketplace.

Related Information

- Information on Heparin (/drugs/postmarket-drug-safety-information-patients-and-providers/information-heparin)
- Comunicado de la FDA sobre la seguridad de los medicamentos: Cambio importante en la etiqueta del envase de heparina para indicar claramente la potencia total del medicamento (/drugs/drug-safety-and-availability/comunicado-de-la-fda-sobre-la-seguridad-de-los-medicamentos-cambio-importante-en-la-etiqueta-del)
INTRODUCTION

For the last four decades, the United States Pharmacopeial Convention (USP) has relied on spontaneous reporting information to support creation of safe medication use and quality of care standards in the *United States Pharmacopeia* (USP) and allied reports. For the most part, these are standards and supporting information that speak to how practitioners within healthcare systems should adjust their processes and practices to promote safe medication use. At times, USP product standards call for the adjustment of labels and labeling to reduce the likelihood of error.¹

As a volunteer-driven, practitioner-based, standards-setting organization, USP provides an important and unique pathway for practitioners to set standards they use in daily life. USP is not itself a regulatory body and does not enforce its standards; however, conformity assessment bodies may recognize USP standards in ways that enhance their value, impact, and at times make them mandatory. Irrespective of their voluntary or mandatory character, standards provide a safe harbor for practitioners and support optimum health care outcomes.

While beyond the scope of this white paper, USP acknowledges—and has always supported—the remarkable work of academia, the Institute of Medicine (IOM), highly involved standards- and conformity-assessment organizations (many of whom are Convention members), and many others who have worked tirelessly to develop information and provide evidence-based approaches to promote patient safety, safe medication use, and optimal quality care. Much of this effort culminated in the seminal reports of the IOM beginning in 1999 and follow-on activities in the IOM and elsewhere.

The Council of the Convention Section on the Quality of Patient Care presents this white paper as a means of reviewing USP’s prior efforts in this area and to encourage the Convention to consider future patient safety opportunities for USP.

¹ For the most part, USP does not provide clinical practice standards, which are the responsibility of practitioner associations, state practice boards, and other certifying bodies.
USP'S LABELING AND NOMENCLATURE RESPONSIBILITIES IN LAW

In the United States, under the Federal Food, Drug, and Cosmetic Act (FDCA), the United States Pharmacopeia (USP) and National Formulary (NF) are recognized as official compendia. A drug with a name recognized in USP-NF must comply with compendial identity standards or risk being deemed adulterated, misbranded, or both. Drugs must also comply with compendial standards for strength, quality, and purity, unless they are labeled to show all respects in which the drug differs. These Federal requirements arise under the adulterated drugs provision of the FDCA at §501(b) as well as the misbranding provisions at §502. The role of nomenclature is particularly important, since the link to drugs “recognized in an official compendium” at §501(b) arises in the statutory provision that addresses the designation of drugs by “established names” at §502(e).

As explained in 21 CFR §299.4, the Food and Drug Administration (FDA) has statutory authority to designate “official” or “established names,” yet it rarely does so. Instead, while continuing to review proprietary (brand) names as part of the drug approval process, FDA defers to USP’s Nomenclature Expert Committee in the Council of Experts and to the U.S. Adopted Names (USAN) Council, in which USP plays a key role, to provide established/nonproprietary drug product and drug substance names. Accordingly, the term “established name” means an article recognized in USP-NF (see FDCA §502(e)(3)), and drugs with such names must meet USP-NF standards for identity as well as (unless labeled otherwise) strength, quality, and purity.

The FDA has extensive authority regarding the labeling of drugs, ranging from the package insert, dispensing, and containers, to advertising and promotional materials. The FDCA provides that a drug with a name recognized in an official compendium—including USP or NF—will be considered misbranded unless it is packaged and labeled as prescribed therein (FDCA §502(g)). Monograph requirements for packaging and labeling are noted in the USP-NF General Notices at 4.10 and are reflected in various monographs and General Chapters.

CURRENT ACTIVITIES

1. THE USP NOMENCLATURE EXPERT COMMITTEE

USP’s Nomenclature Expert Committee establishes nonproprietary names for drug substances, drug products, excipients, biologics, dietary supplements, and medical devices for humans and animals. It also promotes uniformity and consistency among the official titles in the USP and NF. The Committee is concerned with nomenclature for dosage form monographs and other aspects of the language used in the prescription, dispensing, sale, or manufacture of drugs. The Committee works in a collaborative fashion with the USAN Council, and USP has committed to using the USAN as the title of a drug monograph for that substance. The Committee’s authority to develop official nonproprietary names is identified in section 502(e) of the FDCA. The section indicates that a drug is misbranded if its label does not include the “established name” of the drug and each ingredient. It further specifies that the established name of a drug or ingredient is the official title used for the drug or ingredient in an official compendium such as USP or NF, as long as the FDA has not designated an official name in accordance with section 508 of the FDCA. In early 2006, a federal appeals court decision confirmed that the nonproprietary names
assigned by the USP Nomenclature Expert Committee take precedence over the names informally approved by the FDA during regulatory review. Taken together, the public-private partnerships created through Congressional authority have provided U.S. practitioners with coherent non-proprietary drug substance and product names, and these good naming conventions promote safe medication use and quality of care.

2. SAFE MEDICATION USE EXPERT COMMITTEE

The Safe Medication Use Expert Committee (SMU EC) began its work in the 2000-2005 cycle and continued in the 2005-2010 cycle. The nineteen members of the 2005-2010 SMU EC were drawn from the professions of medicine, nursing, and pharmacy, and include representatives from academia, research, government, and consumer interest. In this cycle, the SMU EC has reviewed and analyzed medication error reports submitted to USP, and from those, the Committee established recommendations for revision and development of standards in USP–NF and made recommendations to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) discussed later in this white paper. It also developed guidelines, recommendations, a General Chapter, and publications related to safe medication practices and patient safety. The SMU EC’s members provided support to USP’s two reporting programs—MEDMARX® and the Medication Error Reporting (MER) Program. The SMU EC’s focus has been on policy-level priorities for the safe use of medications and patient safety initiatives. Examples of initiatives appear below:

- **Total Dose per Total Volume** — The SMU EC developed crosscutting support for a requirement to change labeling to indicate total dose per total volume for parenteral packages of 100mL or less. The recommendation was based on errors in which health professionals mistakenly administered the entire vial content in error—published in *Pharmacopeial Forum (PF)* 31(4) [July-Aug 2005]: Strength and Total Volume for Single – and Multiple-Dose Injectable Drug Products.

- **Neuromuscular Blocking Agents** — An article, “Improving the safety of neuromuscular blocking agents: A statement from the USP Safe Medication Use Expert Committee” was published in the *American Journal of Health-System Pharmacists*, Vol 63, Jan 15, 2006. The work stimulated a new policy statement from the American Society of Health-System Pharmacists (ASHP) on the use of neuromuscular blocking agents. The publication of this article followed the standard instituted by USP that required the warning, “Warning – Paralyzing Agent,” on the closures of neuromuscular blocking agents.

- **Patient Safety Stakeholder Forum** — A cross-disciplinary Patient Safety Stakeholder Forum was convened on October 11, 2006 to discern the need for the creation of a new USP publication: “Safe Medication Practices Compendium.” This forum was followed by a USP white paper, “Exploring a Strategic Proposal for the Concept of a Compendium of Safe Medication Practices.” It was eventually concluded that additional exploration was needed to develop such a compendium.

Physical Environments that Promote Safe Medication Use — General Chapter <1066>

Physical Environments that Promote Safe Medication Use was created to provide safe medication use standards for all health care settings.

Guidelines or Standards for Computerized Prescription Order Entry and Other Technologies — The SMU EC is working with Dr. Andrew C. Seger and Dr. Gordon Schiff from Brigham and Women’s Hospital on an analysis of computerized prescription order entry (CPOE) errors from the MEDMARX® database to develop guidelines/standards.

“High Alert Drugs by Location” is being drafted by the Medication Error Data Analysis Advisory Panel of the SMU EC.

Health Literacy and Prescription Container Labeling — The Health Literacy and Prescription Container Labeling Advisory Panel of the SMU EC is working on recommendations for the development of standards regarding simplifying language; using explicit text to describe dosage/intervals, including purpose for use; organizing the label in a patient centered manner; improving readability; and including supplemental information.

Standardized Intravenous Concentrations — The SMU EC completed analysis of a Standard Intravenous (IV) Concentrations survey of health system pharmacy directors in order to determine the standard drip and flush concentrations being used in their respective facilities for the treatment of neonates, pediatrics, and adults. The goal is to standardize product concentrations to help decrease medication errors. The SMU EC will recommend standard concentrations for ten High Alert Drugs as a follow-up to an IV SMU survey (and an IV Summit held at USP) and publish an article identifying standard IV concentrations for ten High Alert Drugs by patient type.

Tall-Man Lettering — The SMU EC will publish an article based, in part, on a research survey titled “Tall Man”/Enhanced Lettering for Medication Name Differentiation. The survey on Tall Man Lettering was conducted in an effort to better understand the current landscape regarding use of and experience with enhanced lettering as a safety tool. Based on the survey results, the USP Nomenclature Expert Committee will consider the advisability of developing standards. A significant number of responses (1,788) were received from pharmacists (60%), nurses (16%), and physicians (16%), with the remainder coming from pharmacy technicians, nurse practitioners, and other healthcare providers. Cooperation in disseminating the survey was obtained primarily from the American Society of Consultant Pharmacists, the ASHP, the Institute for Safe Medication Practices (ISMP), the Joint Commission, and the National Alliance of State Pharmacy Associations.

Harmonization with WHO Label Standards for Vincristine and Other Vinca Alkaloids — Three component changes were recommended to reduce the chance of vincristine (and other vinca alkaloids) being administered by the intrathecal route (which is universally fatal). Through a reworded cautionary statement, the recommendation would change to overwrap alert labeling and add a cautionary statement on the cap and
ferrule of the vial. (This proposal is currently under consideration by the Nomenclature Expert Committee.)

3. THE NATIONAL COORDINATING COUNCIL FOR MEDICATION ERROR REPORTING AND PREVENTION

USP serves as the Secretariat for the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP/The Council), an independent body comprised of numerous national organizations. The Council was formed in 1995 through the efforts of its member associations and agencies to focus on ways to enhance patient safety through a coordinated approach and a systems-based perspective.

An interdisciplinary group of 15 organizations and agencies held its first meeting in July 1995. In the past 14 years, the Council has grown to 26 member organizations and two individual members. The five goals that continue to direct the Council’s activities are:

- Stimulate the development and use of reporting and evaluation systems by individual health care organizations;
- Stimulate reporting to a national system for review, analysis, and development of recommendations to reduce and ultimately prevent medication errors;
- Examine and evaluate the causes of medication errors;
- Increase awareness of medication errors and methods of prevention throughout the health care system; and
- Recommend strategies for system modifications, practice standards and guidelines, and changes in packaging and labeling.

Council Accomplishments—1995 to Present:

- Defined a “medication error” and encouraged all stakeholders to use this definition to provide a uniform basis for medication error reporting and analysis.
- Developed a medication error taxonomy, index and algorithm for categorizing medication errors
- Issued a statement on calculating medication error rates
- Promulgated recommendations for:
  - Prescribing
  - Labeling and packaging
  - Dispensing
  - Administration
USP’S ROLE IN PATIENT SAFETY

- Verbal medication orders
- Standard bar codes on medication packages and containers
- Reducing medication errors in non-health care settings
- Reducing at-risk behaviors
- Bar coding labels to reduce medication errors
- Promoting safe use of drug suffixes
- Avoiding medication errors with drug samples

The Council has had national and international impact through its multidisciplinary conferences on bar coding, drug nomenclature, and suffix use. Continuing activities and other accomplishments include:

1) Developing and disseminating standardized definitions for terms such as *adverse drug event*, *adverse drug reaction*, *harm*, *preventable event*;

2) Establishing a dedicated Web site for organizations, government, and practitioners to reference The Council’s recommendations and other information;

3) Developing a solid oral dosage forms article for broad dissemination;

4) Endorsing the ISMP *Safety Self-Assessment for Community/Ambulatory Pharmacy*;

5) Establishing consumer information links to The Council’s Web site;

6) Developing and disseminating a white paper on the use of bar codes;

7) Signing on to a set of *General Principles* supporting legislation to uphold, as privileged, information submitted to error reporting programs (These *General Principles* were incorporated into the Patient Safety and Quality Improvement Act of 2005 that was signed into law on July 29, 2005);

8) Recognition with the 2007 American Pharmacists Association Foundation Pinnacle Award; and

9) Receipt of the 2008 Eisenberg Award.

In the coming years, The Council will continue to focus on key issues impacting the safe use of medications. With the help of new and enthusiastic member associations and agencies, The Council will address medication reconciliation as well as geriatric and long-term care issues. The members of The Council are recognized at www.nccmerp.org.
PRIOR ACTIVITIES:
USP’S REPORTING PROGRAMS TO SUPPORT STANDARDS

1. DRUG PRODUCT PROBLEM REPORTING PROGRAM

Because of concern with the quality of drug products on the market, in 1971, the USP and the FDA co-founded the Drug Product Problem Reporting Program (DPPR). This was a national program in which health professionals voluntarily reported problems and defects experienced with drug products marketed in the United States. Often, product problems or defects had to do with inadequate packaging or labeling that could lead to errors or confusion on the part of health professionals. Other problems such as inclusion of foreign matter, suspected contamination, questionable potency, and “bioinequivalence” based on observed therapeutic response were also reported among the more than 100,000 observations gathered in DPPR. USP terminated the DPPR contract with the FDA in 1987, but continued a USP Drug Reporting Program until August 2000.

2. MEDICAL DEVICE AND LABORATORY PRODUCT PROBLEM REPORTING PROGRAM

Together with the DPPR Program, USP operated the Medical Device and Laboratory Product Problem Reporting Program (PRP) under contract with the FDA Center for Devices and Radiological Health (CDRH). In this program, USP collected reports on defective medical devices and shared that information with both CDRH and the manufacturers involved in incidents. This program had a major impact on the use of breast implants, dental implants, and marijuana testing kits. It was the precursor to the FDA’s MedWatch program. This contract with the FDA was terminated in September 1995.

3. VETERINARY REPORTING PROGRAM

In 1994, USP established a Veterinary Reporting Program (VRP) to assist the FDA’s Center for Veterinary Medicine (CVM), the Environmental Protection Agency, and the Department of Agriculture in obtaining information about adverse events with veterinary products. Reports were shared with the appropriate government agency and with the manufacturers of the products involved in the reports. The program was terminated in April 2003.

4. MEDICATION ERROR REPORTING PROGRAM

In 1991, USP established its first Medication Error Reporting Program (MER) in conjunction with the ISMP. MER was designed to obtain spontaneous reports both for the medicine itself and the system in which the medicine was prescribed, dispensed, administered, and used. Between 1991 and 2008, MER received more than 6,000 voluntary reports of actual and potential medication errors. MER identified errors in various health care delivery environments, including hospitals, nursing homes, physicians' offices, pharmacies, emergency response vehicles, and home care. The reports documented that errors are multi-disciplinary and multi-factorial and that they may be made by experienced as well as inexperienced health professionals, support personnel, interns, students, and even patients and their caregivers. Medication errors can and regularly do occur anywhere along the continuum from prescribing to transcribing to dispensing and administration. The causes of errors may be attributed to human error, to product names or designs, and to the medication handling and delivery systems in which the products are used and in which individuals operate and interact. USP submitted MER reports to the FDA as a
MedWatch partner, including adverse drug reactions that came to MER but were not evaluated. MER reports were also shared with the relevant manufacturers.

Examples of important changes USP made to its standards as a result of MER reports appear below:

- **Potassium Chloride** — Reported deaths due to the accidental misadministration of concentrated Potassium Chloride Injection led to: 1) changing the official USP name to Potassium Chloride for Injection Concentrate to give more prominence to the need to dilute the product prior to use; 2) requiring that labels bear a boxed warning with the words "Concentrate: Must be Diluted Before Use;" 3) requiring that the cap must be black in color (the use of black caps is restricted to this drug product only); and 4) requiring that the cap must be imprinted in a contrasting color with the words "Must be Diluted."

- **Vincristine Sulfate** — Reported deaths due to confusion and the resultant injection of the anticancer drug, Vincristine Sulfate for Injection, directly into the spine instead of the vein resulted in changes in the requirements for packaging by pharmacies and manufacturers preparing ready-to-use doses. Each dose, whether prepared by the manufacturer or the pharmacist, must now be wrapped in a covering labeled "FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES" and that covering may not be removed until the moment of injection.

- **Amrinone/Amiodarone** — Reported deaths due to the confusion of similar names Amrinone and Amiodarone led USP and the USAN Council to change the nonproprietary name and official title of Amrinone to Inamrinone.

- **Neuromuscular Blocking Agents** — Reported deaths due to the inadvertent mix-up of neuromuscular blocking agents (which paralyze the respiratory system) with other drugs led to recommended changes in standards for labeling and packaging of the therapeutic class of neuromuscular blocking agent products.

5. **MEDMARX®**

MEDMARX® was developed by USP in 1998 as an Internet-accessible, anonymous reporting program that enables hospitals to voluntarily report, track, and trend data, incorporating nationally standardized data elements (i.e., definitions and taxonomy). These standardized elements were drawn from the work of the MER Program, the FDA, NCC MERP, and the ASHP. MEDMARX® is structured to support an interdisciplinary, systems-approach to medication error reduction and fosters a non-punitive environment for reporting. USP created MEDMARX® with the intent to broaden the model to include other health care settings, e.g. long-term and ambulatory care settings, and to include other types of reporting such as medical error and adverse drug reactions.

Hospitals are encouraged to use MEDMARX® as part of their internal quality improvement processes, thereby extending their "peer-review" to other hospitals in the program. Hospitals can review errors entered by other institutions in "real time" and also see any reported action taken by another institution in response to an error in an effort to avoid similar errors in the future.
This feature affords institutions the opportunity to examine errors in a proactive manner. For example, the institution can review the error profile of a drug or class of drugs to determine if certain risk prevention measures or training programs should be established within the institution before a product is added to the institution's formulary. If the error profile is significantly serious, a determination may be made not to stock the drug. MEDMARX® supports the performance improvement standards of the Joint Commission, which requires institutions to look outward at the experiences of others in order to reduce risk.

USP transferred its reporting programs, MEDMARX® and MER, to Quantros and ISMP, respectively, in 2008. USP will continue to use data from these and other programs to enhance its standards-setting activities to promote patient safety and safe medication use. In the interest of public health and to assist practitioners and patients, USP has posted eight annual reports on its Web site free of charge, ensuring full access to this clinically important information.

FUTURE OPPORTUNITIES

1. NOMENCLATURE, SAFETY, AND LABELING EXPERT COMMITTEE FOR THE 2010-2015 CYCLE

   In the next cycle, a new expert committee—Nomenclature, Safety, and Labeling Expert Committee—will combine the work of the Nomenclature and Safe Medication Use Expert Committees from the 2005-2010 cycle. This new Expert Committee will build on the work of its predecessors by continuing to develop guidelines, recommendations, General Chapters, and publications related to safe medication practices and patient safety, as well as by linking these efforts to drug naming and the labeling of medications. Via Expert Panels, specific standards-setting activities can be addressed on a broad range of safe medication use and quality of care standards.

2. INSTITUTE OF MEDICINE

   In 2007, the IOM published Preventing Medication Errors, a report by its Committee on Identifying and Preventing Medication Errors. The report called on USP to work with the FDA and others in several areas related to drug naming, labeling, and packaging. The IOM posited that there are many ways that basic information about a specific drug is communicated to providers and patients and identified some of the more obvious problems:

   - Brand names and generic names that look or sound alike
   - Different formulations of the same brand or generic drug
   - Multiple abbreviations to represent the same concept
   - Confusing word derivatives, abbreviations, and symbols
   - Unclear dose concentration/strength designations
Cluttered labeling—small fonts, poor typefaces, no background contrast, overemphasis on company logos

Inadequate prominence of warnings and reminders

Lack of standardized terminology

The proposed IOM action plan focused on two overarching principles: 1) product naming, labeling, and packaging should be designed for the end user—the provider in the clinical environment and/or the consumer; and 2) safety should always take precedence over commercial interests. In addition, Recommendation #4 of the IOM report included USP in a list of organizations that should work together to address labeling, packaging, and the distribution of free samples.

CONCLUSION

Based on its nomenclature and labeling recognition in the FDCA and exhortations from the community, the need for USP’s involvement in standards to promote safe medication use and quality care is as strong as ever—and may increase in an era of health care crisis and reform. One of USP’s greatest strengths lies in its ability to convene a broad and diverse group of stakeholders around issues common to all, and USP can leverage this role by helping to advance standards related to medication safety that are beyond the scope of a single health profession or professional organization. For many years, USP has devoted substantial resources and energy to its safe medication use and quality of care standards-setting activities, but has struggled to find a sustainable financial and public health model for these activities. Convention Delegates must now ask: What is the appropriate role for USP in setting standards related to medication/patient safety, and how will this role be financially supported? The Council of the Convention Section on the Quality of Patient Care calls on the Convention membership to articulate ways in which a standards-setting body such as USP can continue its work based on USP’s historical contributions, unique capabilities, and current and possible future positions in law.
EXHIBIT 9
INTRODUCTION

Parenteral articles are preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or lesion. Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeial requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration.

NOMENCLATURE AND DEFINITIONS

Nomenclature*

The following nomenclature pertains to five general types of preparations, all of which are suitable for, and intended for, parenteral administration. They may contain buffers, preservatives, or other added substances.

1. [DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.
2. [DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.
3. [DRUG] Injectable Emulsion—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.
4. [DRUG] Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium.
5. [DRUG] for Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

Definitions

PHARMACY BULK PACKAGE

A Pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes.

The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents. The Pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

*This nomenclature has been adopted by the USP Drug Nomenclature Committee for implementation by supplemental revisions of USP 23-NF 18. For currently official monograph titles in the form Sterile [DRUG] that have not yet been revised, the following nomenclature continues in use in this Pharmacopeia: (1) medicaments or solutions or emulsions thereof suitable for injection, bearing titles of the form [DRUG] Injection; (2) dry solids or liquid concentrates containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for Injections, and which are distinguished by titles of the form [DRUG] for Injection; (3) dry solids which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile Suspensions, and which are distinguished by titles of the form Sterile [DRUG] for Suspension.

Vehicles and Added Substances

Aqueous Vehicles—The vehicles for aqueous Injections meet the requirements of the Pyrogen Test (151) or the Bacterial Endotoxins Test (85), whichever is specified. Water for Injection generally is used as the vehicle, unless otherwise specified in the individual monograph. Sodium chloride may be added in amounts sufficient to render the resulting solution isotonic; and Sodium Chloride Injection, or Ringer’s Injection, may be used in whole or in part instead of Water for Injection, unless otherwise specified in the individual monograph. For conditions applying to other adjuvants, see Added Substances in this chapter.

Other Vehicles—Fixed oils used as vehicles for nonaqueous Injections of vegetable origin, are odorless or nearly so, and have no odor suggesting rancidity. They meet the requirements of the test for Solid paraffin under Mineral Oil, the cooling bath being maintained at 10°, have a Saponification Value between 185 and 200 (see Fats and Fixed Oils (401)), have an Iodine Value between 79 and 141 (see Fats and Fixed Oils (401)), and meet the requirements of the following tests.

Unsaponifiable Matter—Reflux on a steam bath 10 mL of the oil with 15 mL of sodium hydroxide solution (1 in 6) and 30 mL of alcohol, with occasional shaking until the mixture becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 mL of water; a clear solution results.

Free Fatty Acids—The free fatty acids in 10 g of oil require for neutralization not more than 2.0 mL of 0.020 N sodium hydroxide (see Fats and Fixed Oils (401)).

Synthetic mono- or diglycerides of fatty acids may be used as vehicles, provided they are liquid and remain clear when cooled to 10° and have an Iodine Value of not more than 140 (see Fats and Fixed Oils (401)).

These and other nonaqueous vehicles may be used, provided they are safe, in the volume of Injection administered, and also provided they do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

Added Substances—Suitable substances may be added to preparations intended for injection to increase stability or usefulness, un-
less proscribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with the therapeutic efficacy or with the responses to the specified assays and tests. No coloring agent may be added solely for the purpose of coloring the finished preparation, to a solution intended for parenteral administration (see also Added Substances under General Notices and Antimicrobial Effectiveness Testing (51)).

Observe special care in the choice and use of added substances in preparations for injection that are administered in a volume exceeding 5 mL. The following maximum limits prevail unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01%; for chlorobutanol, cresol, phenol, and similar types of substances, 0.5%; and for sulfur dioxide, or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%. A suitable substance or mixture of substances to prevent the growth of microorganisms must be added to preparations intended for injection that are packaged in multiple-dose containers, regardless of the method of sterilization employed, unless one of the following conditions prevails: (1) there are different directions in the individual monograph; (2) the substance contains a radionuclide with a physical half-life of less than 24 hours; and (3) the active ingredients are themselves antimicrobial. Such substances are used in concentrations that will prevent the growth of or kill microorganisms in the preparations for injection. Such substances also meet the requirements of Antimicrobial Effectiveness Testing (51) and Antimicrobial Agents—Content (341). Sterilization processes are employed even though such substances are used (see also Sterilization and Sterility Assurance of Compendial Articles (1211)). The air in the container may be evacuated or be displaced by a chemically inert gas. Where specified in a monograph, information regarding sensitivity of the article to oxygen is to be provided in the labeling.

**LABELS AND LABELING**

**Labeling**

**NOTE—**See definitions of “label” and “labeling” in Labeling in the section Preservation, Packaging, Storage, and Labeling of the General Notices and Requirements.

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of active ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect. The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

**STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS**

For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL.

- The following formats are acceptable for contents greater than 1 mL:
  - Total strength/total volume: 500 mg/10 mL
  - Strength/mL: 50 mg/mL
  - Total strength/total volume: 25,000 Units/5 mL
  - Strength/mL: 5,000 Units/mL

- The following format is acceptable for contents of less than 1 mL: 12.5 mg/0.625 mL

There are, however, some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be effective in preventing medication errors (e.g., insulin). An example is the use of lidocaine or other similar drugs used as a local anesthetic where the product is ordered and administered by percentage (e.g., 1%, 2%) or a local anesthetic in combination with epinephrine that is expressed as a ratio (e.g., 1:100,000). In such cases, the total strength should be expressed: for example, 1% (100 mg/10 mL). Dry solids, which need to be reconstituted, should follow the same format, with the exception that only the total strength of the drug should be listed, not the strength/total volume or strength/mL.

(Official February 1, 2009)

**Aluminum in Large-Volume Parenterals (LVPs), Small-Volume Parenterals (SVPs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy**

- The aluminum content of LVPs used in TPN therapy must not exceed 25 µg per L (µg/L).
- The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the “Precautions” section of the labeling of all LVPs used in TPN therapy.
- If the maximum amount of aluminum in SVPs and PBPs is 25 µg per L (µg/L) or less, instead of stating the exact amount of aluminum that each contains, as in paragraph (d), the immediate container label for SVPs and PBPs used in the preparation of TPN parenterals (with exceptions as noted below) may state: “Contains no more than 25 µg/L of aluminum”. If the SVP or PBP is a lyophilized powder, the immediate container label may state the following: “When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L”.
- The maximum level of aluminum at expiry must be stated on the immediate container label of all SVPs and PBPs used in the preparation of TPN parenterals and injectable emulsions. The aluminum content must be stated as follows: “Contains no more than ___ µg/L of aluminum”. The immediate container label of all SVPs and PBPs that are lyophilized powder used in the preparation of TPN solutions must contain the fol-
following statement: “When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than __ µg/L.” This maximum amount of aluminum must be stated as the highest one of the following three levels:

(1) The highest level for the batches produced during the last three years
(2) The highest level for the latest five batches
(3) The maximum level in terms of historical levels, but only until completion of production of the first five batches after July 26, 2004.

The package insert for all LVPs, SVPs, and PBPUs used in the preparation of TPN products must contain a warning statement. This warning must be contained in the “Warning” section of the labeling and must state the following: “WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products.”

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see Containers—Plastics (661)).

For definitions of single-dose and multiple-dose containers, see Containers in the General Notices and Requirements. Containers meet the requirements under Containers—Glass (660) and Containers—Plastics (661).

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient’s body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an am-
pul is prohibited, except for Potassium Chloride for Injection Concentrate.

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: “Warning: Paralyzing Agent” or “Paralyzing Agent” (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the Assay in a monograph provides a procedure for the Assay preparation, in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled “size” or that volume which is to be withdrawn. See Injections under Pharmaceutical Dosage Forms (1151).

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Suspensions and emulsions must be shaken before withdrawal of the contents and before the determination of the density. Oily and viscous preparations may be warmed according to the instructions on the label, if necessary, and thoroughly shaken immediately before removing the contents. The contents are then cooled to 20°–25°C before measuring the volume.

Single-Dose Containers—Select 1 container if the volume of the container is 10 mL or more, 3 containers if the nominal volume is more than 3 mL and less than 10 mL, or 5 containers if the nominal volume is 3 mL or less. Take up individually the total contents of each container selected into a dry syringe of a capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of its graduated volume. Alternatively, the volume of the contents in mL may be calculated as the mass, in g, divided by the density. For containers with a nominal volume of 2 mL or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement, provided that a separate, dry syringe assembly is used for each container. The contents of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.
Injections packaged for intravascular use that may be used for intermittent, continuous, or bolus replacement fluid administration during hemodialysis or other procedures, unless excepted above, must conform to the 1-L restriction.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

FOREIGN AND PARTICULATE MATTER

All articles intended for parenteral administration shall be prepared in a manner designed to exclude particulate matter as defined in Particulate Matter in Injections (788) and other foreign matter. Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed “visible particulates”) in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates. Qualification of the inspection process shall be performed with reference to particulates in the visible range of a type that might emanate from the manufacturing or filling process. Every container whose contents shows evidence of visible particulates shall be rejected. The inspection for visible particulates may take place when inspecting for other critical defects, such as cracked or defective containers or seals, or when characterizing the appearance of a lyophilized product.

Where the nature of the contents or the container-closure system permits only limited capability for the inspection of the total contents, the 100% inspection of a lot shall be supplemented with the inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container) contents of a sample of containers from the lot.

All large-volume Injections for single-dose infusion and small-volume Injections are subject to the light obscuration or microscopic procedures and limits for subvisible particulate matter set forth in Particulate Matter In Injections (788), unless otherwise specified in the individual monograph. An article packaged as both a large-volume and a small-volume Injection meets the requirements set forth for small-volume Injections where the container is labeled as containing 100 mL or less, if the individual monograph states a test for Particulate Matter (788); it meets the requirements set forth for large-volume Injections for single-dose infusion where the container is labeled as containing more than 100 mL. Injections administered exclusively by the intramuscular or subcutaneous route or packaged and labeled for use as irrigating solutions are exempt from requirements for Particulate Matter (788).

STERILITY

Sterility Tests—Preparations for injection meet the requirements under Sterility Tests (71).

CONSTITUTED SOLUTIONS

Dry solids from which constituted solutions are prepared for injection bear titles of the form [DRUG] for Injection. Because these dosage forms are constituted at the time of use by the health care practitioner, tests and standards pertaining to the solution as constituted for administration are not included in the individual monographs on sterile dry solids or liquid concentrates. However, in the interest of assuring the quality of injection preparations as they are actually administered, the following nondestructive tests are provided for demonstrating the suitability of constituted solutions when they are prepared just prior to use.

Completeness and Clarity of Solution—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form.

A: The solid dissolves completely, leaving no visible residue as undissolved matter.

B: The constituted solution is not significantly less clear than an equal volume of the diluent or of Purified Water contained in a similar vessel and examined similarly.
Particulate Matter—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.
Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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)

December 2018
Biosimilars

Revision 1
Questions and Answers on Biosimilar Development and the BPCI Act

Guidance for Industry

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U.S. Department of Health and Human Services
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Revision 1
# TABLE OF CONTENTS

- **INTRODUCTION** ........................................................................................................................................ 1
- **BACKGROUND** ....................................................................................................................................... 3
- **QUESTIONS AND ANSWERS** ................................................................................................................ 5  
  I. BIOSIMILARITY OR INTERCHANGEABILITY ....................................................................................... 5  
  II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT” ................................................................................................................................. 17  
  III. EXCLUSIVITY ...................................................................................................................................... 19
Questions and Answers on Biosimilar Development and the BPCI Act
Guidance for Industry

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

INTRODUCTION

This guidance document provides answers to common questions from prospective applicants and other interested parties regarding the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The question and answer (Q&A) format is intended to inform prospective applicants and facilitate the development of proposed biosimilars and interchangeable biosimilars, as well as to describe FDA’s interpretation of certain statutory requirements added by the BPCI Act.

The BPCI Act amended the Public Health Service Act (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) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA’s interpretation of the BPCI Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q&As respond to questions the Agency has received from prospective applicants regarding the appropriate statutory authority under which certain products will be regulated. FDA intends to update this guidance document to include additional Q&As as appropriate.

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1 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).

We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

2 In this guidance, the following terms are used to describe biological products licensed under section 351(k) of the PHS Act: (1) biosimilar or biosimilar product refers to a product that FDA has determined to be biosimilar to the reference product (see sections 351(i)(2) and 351(k)(2) of the PHS Act) and (2) interchangeable biosimilar or interchangeable product refers to a biosimilar product that FDA has determined to be interchangeable with the reference product (see sections 351(i)(3) and 351(k)(4) of the PHS Act). Biosimilarity, interchangeability, and related issues are discussed in more detail in the Background section of this guidance.
Contains Nonbinding Recommendations

This guidance document revises the final guidance document entitled *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, to clarify and update certain Q&As and to add new Q&As. For certain Q&As, FDA has updated the Q&A by abbreviating the answer and, where appropriate, referring the reader to a separate guidance document that provides additional information on the topic. Alternatively, FDA may have withdrawn a Q&A if the topic is addressed in a separate guidance document or if FDA determined that the Q&A should be revised in some respect and reissued. Additional information about the Q&A format for this guidance document is provided in the Background section.

FDA is also issuing a draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*. When finalized, this draft guidance document will be part of a series of guidance documents that FDA has developed to facilitate development of biosimilar and interchangeable products. The final guidance documents issued to date address a broad range of issues, including:

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)
- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (December 2016)
- Labeling for Biosimilar Products (July 2018)

In addition, FDA has published draft guidance documents related to the BPCI Act, which, when finalized, will represent FDA’s current thinking. These draft guidance documents include:

- New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018)
- Considerations in Demonstrating Interchangeability With a Reference Product (January 2017)
- Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (June 2018)
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (August 2014)
In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

**BACKGROUND**

*The BPCI Act*

The BPCI Act was enacted as part of the ACA on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the ACA). Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar or interchangeable product.

Section 351(i) defines the term *biosimilar* or *biosimilarity* “in reference to a biological product that is the subject of an application under [section 351(k)]” to mean “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” (see section 351(i)(2) of the PHS Act).

Section 351(k)(4) of the PHS Act provides that upon review of an application submitted under section 351(k) or any supplement to such application, FDA will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application (or a supplement to such application) is sufficient to show that the biological product “is biosimilar to the reference product” and “can be expected to produce the same clinical result as the reference product in any given patient” and that “for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”

Section 351(i) of the PHS Act states that the term *interchangeable* or *interchangeability*, in reference to a biological product that is shown to meet the standards described in section 351(k)(4) of the PHS Act, means that “the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

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3 *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 (section 351(i)(4) of the PHS Act).
4 Section 351(k)(4)(A) of the PHS Act.
5 Section 351(k)(4)(B) of the PHS Act.
In this guidance document, the terms *proposed biosimilar product* and *proposed interchangeable product* are used to describe products that are under development or are the subject of a pending 351(k) biologics license application (BLA).

Certain other provisions of the BPCI Act are discussed in the context of the relevant Q&A.

**“Question and Answer” Guidance Format**

This final guidance document is a companion to the draft guidance document entitled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)*. In this pair of guidance documents, FDA issues each Q&A in draft form in the draft guidance document, receives comments on the draft Q&A, and, as appropriate, moves the Q&A to this final guidance document after reviewing comments and incorporating suggested changes to the Q&A, when appropriate. A Q&A that was previously in the final guidance document may be withdrawn and moved to the draft guidance document if FDA determines that the Q&A should be revised in some respect and reissued in the draft Q&A guidance document. A Q&A also may be withdrawn and removed from the Q&A guidance documents if, for instance, the issue addressed in the Q&A is addressed in another FDA guidance document.

A reference will follow each question in this final guidance document describing the publication date of the current version of the Q&A, and whether the Q&A has been added to or modified in this final guidance document. FDA has maintained the original numbering of the Q&As used in the April 2015 final guidance document (*Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*) and May 2015 draft guidance document (*Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*). For ease of reference, a Q&A retains the same number when it moves from the draft guidance document to the final guidance document and, where appropriate, when a Q&A is withdrawn from the final guidance document and moved to the draft guidance document.

Where a Q&A has been withdrawn from the final guidance document, this is marked in the final guidance document by several asterisks between nonconsecutively numbered Q&As and, where appropriate, explanatory text.
QUESTIONS AND ANSWERS

I. BIOSIMILARITY OR INTERCHANGEABILITY

Q. I.1. *Whom should a sponsor contact with questions about its proposed development program for a proposed biosimilar product or a proposed interchangeable product?*

[A. I.1. FDA provides current contact information on its website. See FDA’s website, “Biosimilars,” available at https://www.fda.gov/biosimilars and click on the link, “Industry Information and Guidance” listed in the left column.

Q. I.2. *When should a sponsor request a meeting with FDA to discuss its development program for a proposed biosimilar product or a proposed interchangeable product, and what data and information should a sponsor provide to FDA as background for this meeting?*

[A. I.2. See FDA’s draft guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* for a description of the different meeting types intended to facilitate biosimilar development programs in accordance with the Biosimilar User Fee Act of 2012 (BsUFA), as reauthorized by the Biosimilar User Fee Amendments of 2017 (BsUFA II) and the criteria/data needed to support the request. The type of meeting granted will depend on the stage of product development and whether the information submitted in the meeting package meets the criteria for the type of meeting.

Q. I.3. *Can a proposed biosimilar product have a formulation that is different from the reference product?*

[A. I.3. Differences between the formulation of a proposed biosimilar product and the reference product may be acceptable. A 351(k) application must contain information demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components. In addition, an applicant would need to demonstrate that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. It may be possible, for example, for a proposed biosimilar product formulated without human serum albumin to demonstrate biosimilarity to a reference product formulated with human serum albumin. For more information about FDA’s current thinking on

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6 This draft guidance, when finalized, will represent FDA’s current thinking on this topic.
the interpretation of the statutory standard for biosimilarity, see FDA’s guidances for industry on *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* and *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.*

**Q. I.4.** *Can a proposed biosimilar product have a delivery device or container closure system that is different from its reference product?*  
*Updated/Retained in Final December 2018*

**A. I.4.** Some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable. It may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled syringe or in an auto-injector device (which are considered the same dosage form), even if the reference product is licensed in a vial presentation, provided that the proposed biosimilar product meets the statutory standard for biosimilarity and adequate performance data for the delivery device or container closure system are provided. For a proposed biosimilar product in a different delivery device or container closure system, the delivery device or container closure system must be shown to be compatible for use with the final formulation of the biological product through appropriate studies, including, for example, extractable/leachable studies and stability studies. Also, for design differences in the delivery device or container closure system, performance testing and a human factors study may be needed.

However, an applicant will not be able to obtain licensure of a proposed biosimilar product when a design difference in the delivery device or container closure system results in any of the following:

- A clinically meaningful difference between the proposed biosimilar product and the reference product in terms of safety, purity, and potency;
- A different route of administration or dosage form; or
- A condition of use (e.g., indication, dosing regimen) for which the reference product has not been previously approved; or otherwise does not meet the standard for biosimilarity.

A proposed biosimilar product in a delivery device will be considered a combination product and may, in some instances, require a separate application for the device.

For information about a delivery device or container closure system for a proposed interchangeable product, see FDA’s draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product.*

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7 This draft guidance, when finalized, will represent FDA’s current thinking on this topic.
Q. I.5. **Can an applicant obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed?**

[A. I.5. Issued April 2015]

Yes, an applicant may obtain licensure of a proposed biosimilar product for fewer than all routes of administration for which an injectable reference product is licensed. An applicant must demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product in terms of safety, purity, and potency. In a limited number of circumstances, this may include providing information from one or more studies using a route of administration for which licensure is not requested (e.g., a study using subcutaneous administration may provide a more sensitive comparative assessment of immunogenicity of the reference product and a proposed biosimilar product, even though licensure of the proposed biosimilar product is requested only for the intravenous route of administration).

Q. I.6. **Can an applicant obtain licensure of a proposed biosimilar product for fewer than all presentations (e.g., strengths or delivery device or container closure systems) for which a reference product is licensed?**

[A. I.6. Updated/Retained in Final December 2018]

An applicant is not required to obtain licensure of a proposed biosimilar product for all presentations for which the reference product is licensed. However, if an applicant seeks licensure for a particular indication or other condition of use for which the reference product is licensed and that indication or condition of use corresponds to a certain presentation of the reference product, the applicant may need to seek licensure for that particular presentation (see also questions and answers 1.4 and 1.5).

Q. I.7. **Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?**

[A. I.7. Updated/Retained in Final December 2018]

An applicant generally may obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed. The 351(k) application must include information demonstrating that the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling submitted for the proposed biosimilar product have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).
For information about the licensure of a proposed interchangeable product, see FDA’s draft guidance for industry, Considerations in Demonstrating Interchangeability With a Reference Product. 8

Q. I.8. *Can a sponsor use comparative animal or clinical data with a non-U.S.-licensed product to support a demonstration that the proposed product is biosimilar to the reference product?*

[Updated/Retained in Final December 2018]

A. I.8. A sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed.

If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The acceptability of such an approach will be evaluated on a case-by-case basis, and should be discussed in advance with the Agency. For certain complex biological products, a modified approach may be needed. A final determination about the adequacy of the scientific justification and bridge will be made during the review of the application.

Issues that a sponsor may need to address to use a non-U.S.-licensed comparator product in a biosimilar development program include, but are not limited to, the following:

- The relevance of the design of the clinical program to support a demonstration of biosimilarity to the U.S.-licensed reference product for the condition(s) of use and patient population(s) for which licensure is sought;

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8 This draft guidance, when finalized, will represent FDA’s current thinking on this topic.
The relationship between the license holder for the non-U.S.-licensed comparator product and BLA holder for the U.S.-licensed reference product;

Whether the non-U.S.-licensed comparator product was manufactured in a facility(ies) licensed and inspected by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries);

Whether the non-U.S.-licensed comparator product was licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., ICH countries) and the duration and extent to which the product has been marketed; and

The scientific bridge between the non-U.S.-licensed comparator product and the U.S.-licensed reference product, including comparative physicochemical characterization, biological assays/functional assays, degradation profiles under stressed conditions, and comparative clinical PK and, when appropriate, PD data, to address the impact of any differences in formulation or primary packaging on product performance.

A sponsor should also address any other factors that may affect the relevance of comparative data with the non-U.S.-licensed comparator product to an assessment of biosimilarity with the U.S.-licensed reference product.

A sponsor may submit publicly available information regarding the non-U.S.-licensed comparator product to justify the extent of comparative data needed to establish a bridge to the U.S.-licensed reference product. The complexity of the products, particularly with respect to higher order structure, post-translational modifications (e.g., glycosylation), and the degree of heterogeneity associated with the product may affect the considerations for the scientific justification regarding the extent of bridging data. Additional factors that FDA may consider regarding the extent of bridging data include, but are not limited to, the following:

Whether the formulation, dosage form, and strength of the U.S.-licensed reference product and non-U.S.-licensed comparator products are the same;

The route of administration of the U.S.-licensed reference product and non-U.S.-licensed comparator products;

The design of the physicochemical and biological/functional assessments and the use of multiple orthogonal methods with adequate sensitivity to detect differences among the products;
The scientific justification for the selection of the non-U.S.-licensed comparator lots used to establish the scientific bridge and how the selected lots relate to the material used in the nonclinical and clinical studies. The scientific bridge should include a sufficient number of lots of non-U.S.-licensed comparator product to adequately capture the variability in product quality attributes. When possible, the non-U.S.-licensed comparator lots used in the nonclinical or clinical studies should be included in the assessment performed to establish the analytical bridge.

Sponsors are encouraged to discuss with FDA during the development program the adequacy of the scientific justification and bridge to the U.S.-licensed reference product. A final decision about the adequacy of this scientific justification and bridge will be made by FDA during review of the 351(k) application.

For more information about whether a non-U.S.-licensed comparator can be used in studies intended to support the additional criteria required for a determination of interchangeability with the reference product, see FDA’s draft guidance for industry, Considerations in Demonstrating Interchangeability With a Reference Product.9

Q. I.9. Is a clinical study to assess the potential of the biological product to delay cardiac repolarization (a QT/QTc study) or a drug-drug interaction study generally needed for licensure of a proposed biosimilar product?
[Moved to Final from Draft December 2018]

A. I.9. In general, a 351(k) application for a proposed biosimilar product may rely upon the Agency’s previous determination of safety, purity, and potency for the reference product, including any clinical QT/QTc interval prolongation and proarrhythmic potential and drug-drug interactions. If such studies were not required for the reference product, then these data generally would not be needed for licensure of a proposed biosimilar product under section 351(k) of the PHS Act. However, if the BLA holder for the reference product has been required to conduct postmarket studies or clinical trials under section 505(o)(3) of the Federal Food, Drug and Cosmetic Act (FD&C Act) to assess or identify a certain risk related to a QT/QTc study or a drug-drug interaction study and those studies have not yet been completed, then FDA may impose similar postmarket requirements on the 351(k) applicant in appropriate circumstances.

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9 This draft guidance, when finalized, will represent FDA’s current thinking on this topic.
Q. I.10. How long and in what manner should sponsors retain reserve samples of the biological products used in comparative clinical PK and/or PD studies intended to support a 351(k) application?

[Moved to Final from Draft December 2018]

A. I.10. Reserve samples establish the identity of the products tested in the actual study, allow for confirmation of the validity and reliability of the results of the study, and facilitate investigation of further follow-up questions that arise after the studies are completed. FDA recommends that the sponsor of a proposed biosimilar product retain reserve samples for at least 5 years following the date on which the 351(k) application is licensed, or, if such application is not licensed, at least 5 years following the date of completion of a comparative clinical PK and/or PD study of the reference product and the proposed biosimilar product (or other clinical study in which PK or PD samples are collected with the primary objective of assessing PK or PD similarity) that is intended to support a submission under section 351(k) of the PHS Act. Contact the FDA for specific advice if an alternative approach is being considered. For a 3-way PK similarity study, FDA recommends that samples of both comparator products be retained, in addition to samples of the proposed biosimilar product.

For most protein therapeutics, FDA recommends that a sponsor retain the following quantities of product and dosage units, which are expected to be sufficient for evaluation by state of the art analytical methods:

- A minimum of 10 dosage units each of the proposed biosimilar product, reference product and, if applicable, non-U.S.-licensed comparator product, depending on the amount of product within each unit. In general, this should provide for a total product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL.

FDA recommends that the sponsor contact the review division to discuss the appropriate quantities of reserve samples in the following situations:

- A product mass of equal to or greater than 200 mg in a volume equal to or greater than 10 mL requires a large number of dosage units.
- Biological products other than protein therapeutics.

Q. I.11. This question and answer have been withdrawn. For information on extrapolation, see FDA’s guidance for industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

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Contains Nonbinding Recommendations

Q.I.12. This question and answer have been withdrawn and moved to FDA’s draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).*

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Q. I.13. *What constitutes “publicly-available information” regarding FDA’s previous determination that the reference product is safe, pure, and potent to include in a 351(k) application?* [Moved to Final from Draft December 2018]

A. I.13. “Publicly-available information” in this context generally includes the current FDA-approved labeling for the reference product and the types of information found in the “action package” for a BLA (see section 505(l)(2)(C) of the FD&C Act). However, FDA notes that submission of publicly available information composed of less than the current FDA-approved labeling for the reference product and the action package for the reference product BLA will generally not be considered a bar to submission or approval of an acceptable 351(k) application.

FDA intends to post on the Agency’s Web site publicly available information regarding FDA’s previous determination of safety, purity, and potency for certain biological products to facilitate biosimilar development programs and submission of 351(k) applications. We note, however, that the publicly available information posted by FDA in this context does not necessarily include all information that would otherwise be disclosable in response to a Freedom of Information Act request.

Q. I.14. *Can an applicant obtain a determination of interchangeability between its proposed product and the reference product in an original 351(k) application?* [Moved to Final from Draft December 2018]

A. I.14. Yes. For more information, see FDA’s draft guidance for industry, *Considerations in Demonstrating Interchangeability With a Reference Product.*

Q. I.15. *Is a pediatric assessment under the Pediatric Research Equity Act (PREA) required for a proposed biosimilar product?* [Updated/Retained in Final December 2018]

A. I.15. Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the

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10 This draft guidance, when finalized, will represent FDA’s current thinking on this topic.
product for the claimed indication unless this requirement is waived, deferred, or inapplicable.  

Section 505B(l) of the FD&C Act\textsuperscript{12} provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a “new active ingredient” for purposes of PREA. However, if an applicant first seeks licensure of its proposed product as a biosimilar product, the applicant must address applicable PREA requirements for its non-interchangeable biosimilar product even if it ultimately intends to subsequently seek licensure of the product as an interchangeable product.

See question and answer I.16 in the draft guidance for industry, \textit{New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)}, for information on how a proposed biosimilar product applicant may fulfill the requirement for pediatric assessments under PREA.

FDA encourages prospective biosimilar applicants to submit plans for pediatric studies as early as practicable during product development. If there is no active investigational new drug application (IND) for the proposed biosimilar product and the sponsor intends to conduct a comparative clinical study as part of its development program, the initial pediatric study plan (PSP) should be submitted as a pre-IND submission. In this scenario, FDA encourages the sponsor to meet with FDA before submission of the initial PSP to discuss the details of the planned development program. It is expected that the sponsor will submit the initial PSP before initiating any comparative clinical study in its biosimilar development program. For more information see question and answer I.17 of this guidance. See also the draft guidance for industry, \textit{Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016)}.\textsuperscript{13}

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\textsuperscript{11} Section 505B(a)(1) was amended in 2017 by section 504 of the Food and Drug Administration Reauthorization Act (FDARA) (\textit{Public Law 115-52}) (August 18, 2017) to include requirements for the submission of molecularly targeted pediatric cancer investigations for certain applications submitted on or after August 18, 2020, under section 505 of the FD&C Act or section 351 of the PHS Act. These requirements are not specifically addressed in this guidance.

\textsuperscript{12} The statutory provision that appears in section 505(l) of the FD&C Act was originally enacted as section 505(n) of the FD&C Act (as amended by the BPCI Act on March 23, 2010). The provision was subsequently redesignated as 505(m) of the FD&C Act. See section 501(b) of the Food and Drug Administration Safety and Innovation Act (\textit{Public Law 112-144}) (July 9, 2012). The provision was redesignated again as section 505(l). See section 3102(3) of the 21st Century Cures Act (\textit{Public Law 114-255}) (December 13, 2016).

\textsuperscript{13} This guidance, when finalized, will provide FDA’s current thinking on issues related to pediatric study plans.
Q. I.17. When should a proposed biosimilar product applicant submit an initial pediatric study plan (PSP)?  
[Moved to Final from Draft December 2018]

A. I.17. Section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires applicants subject to the Pediatric Research Equity Act (PREA) to submit an initial pediatric study plan (PSP) no later than 60 calendar days after the date of an end-of-Phase 2 (EOP2) meeting, or at another time agreed upon by FDA and the applicant. FDA has issued draft guidance on the PSP process, including the timing of PSP submission. 14

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process for reaching agreement between an applicant and FDA on an initial PSP that generally lasts up to 210 days. Given the potential length of this process, and in the absence of an EOP2 meeting for a proposed biosimilar product, FDA recommends that if a sponsor has not already initiated a comparative clinical study intended to address the requirements under section 351(k)(2)(A)(i)(I)(cc) of the Public Health Service (PHS) Act, the sponsor should submit an initial PSP as soon as feasible, but no later than 210 days before initiating such a study. This is intended to provide adequate time to reach agreement with FDA on the initial PSP before the study is initiated. Depending on the details of the clinical program, it may be appropriate to submit an initial PSP earlier in development. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP.

For additional guidance on submission of the PSP, including a PSP Template, please refer to: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

Q. I.18 For biological products intended to be injected, how can an applicant demonstrate that its proposed biosimilar product has the same “dosage form” as the reference product?  
[Moved to Final from Draft December 2018]

A. I.18. Under section 351(k)(2)(A)(i)(IV) of the PHS Act, an applicant must demonstrate that the dosage form of the proposed biosimilar or interchangeable product is the same as that of the reference product. For purposes of implementing this statutory

14 See the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (March 2016). This draft guidance, when finalized, will provide FDA’s current thinking on this topic.
provision, FDA considers the \textit{dosage form} to be the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. In the context of proposed biosimilar products intended to be injected, FDA considers, for example, “injection” (e.g., a solution) to be a different dosage form from “for injection” (e.g., a lyophilized powder). Thus, if the dosage form of the reference product is “injection,” an applicant could not obtain licensure of a proposed biosimilar product with a dosage form of “for injection” even if the applicant demonstrated that the proposed biosimilar product, when constituted or reconstituted, could meet the other requirements for an application for a proposed biosimilar product.

For purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act, FDA also considers emulsions and suspensions of products intended to be injected to be distinct dosage forms. Liposomes, lipid complexes, and products with extended-release characteristics present special scenarios due to their unique composition, and prospective applicants seeking further information should contact FDA.

It should be noted, however, that this interpretation regarding the same dosage form is for purposes of section 351(k)(2)(A)(i)(IV) of the PHS Act only. For example, this interpretation should not be cited by applicants seeking approval of a new drug application under section 505(c) of the FD&C Act, approval of an abbreviated new drug application under section 505(j) of the FD&C Act, or licensure of a BLA under section 351(a) of the PHS Act for purposes of determining whether separate applications should be submitted and assessed separate fees for different dosage forms.

\textbf{Q. I.19. } If a non-U.S.-licensed product is proposed for importation and use in the U.S. in a clinical investigation intended to support licensure of a proposed product under section 351(k) (e.g., a bridging clinical PK and/or PD study), is a separate IND required for the non-U.S.-licensed product? [Moved to Final from Draft December 2018]

\textbf{A. I.19. } A sponsor may submit a single IND for a development program that is intended to support licensure of a proposed product under section 351(k) of the PHS Act and includes use of a non-U.S.-licensed product. The sponsor should submit information supporting the proposed clinical investigation with the non-U.S.-licensed comparator product under the IND. This scenario may occur, for example, if a sponsor seeks to use data from a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, and proposes to conduct a clinical PK and/or PD study in the U.S. with all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed product) to support establishment of a bridge between all three products and scientific justification for the relevance of these comparative data to an assessment of biosimilarity to the U.S.-licensed reference product.
A non-U.S.-licensed comparator product is considered an investigational new drug in the United States, and thus would require an IND for importation and use in the United States (see 21 CFR 312.110(a)). If a sponsor intends to conduct a clinical investigation in the United States using a non-U.S.-licensed comparator product, the IND requirements in 21 CFR part 312 also would apply to this product (see, e.g., 21 CFR 312.2).

With respect to chemistry, manufacturing, and controls (CMC) information, a sponsor should submit to the IND as much of the CMC information required by 21 CFR 312.23(a)(7) as is available. However, FDA recognizes that a sponsor may not be able to obtain all of the CMC information required by 21 CFR 312.23(a)(7) for a non-U.S.-licensed comparator product for which it is not the manufacturer. In these circumstances, the sponsor can request in an IND submission that FDA waive the regulatory requirements related to CMC information on the non-U.S.-licensed comparator product (21 CFR 312.10). The waiver request must include at least one of the following:

- An explanation why compliance with the requirements of 21 CFR 312.23(a)(7) is unnecessary or cannot be achieved;
- Information that will satisfy the purpose of the requirement by helping to ensure that the investigational drug will have the proper identity, strength, quality, and purity; or
- Other information justifying a waiver.15

Information that is relevant to whether the investigational drug will have the proper identity, strength, quality, and purity may include, for example, information indicating whether the investigational drug has been licensed by a regulatory authority that has similar scientific and regulatory standards as FDA (e.g., International Conference on Harmonisation (ICH) countries). This should include, to the extent possible, summary approval information and current product labeling made public by the foreign regulatory authority. In addition, a sponsor should also provide information on the conditions and containers that will be used to transport the drug product to the US clinical site(s) and information on the relabeling and repackaging operations that will be used to relabel the drug product vials for investigational use. This should include information on how exposure of the product to light and temperature conditions outside of the recommended storage conditions will be prevented. A risk assessment on the impact the relabeling operations may have on drug product stability should also be included.

The sponsor should consult with the appropriate FDA review division regarding the CMC information necessary to support the proposed clinical study.

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15 See 21 CFR 312.10(a).
As would be applicable to all investigational drugs, FDA reminds sponsors that the investigator brochure (IB) for studies to be conducted under the IND should be carefully prepared to ensure that it is not misleading, erroneous, or materially incomplete, which can be a basis for a clinical hold (see 21 CFR 312.42(b)(1)(iii) and (b)(2)(i)). For example, the term reference product should be used in the IB only to refer to the single biological product licensed under section 351(a) of the PHS Act against which the proposed product is evaluated for purposes of submitting a 351(k) application. The IB and study protocol(s) should use consistent nomenclature that clearly differentiates the proposed product from the reference product. The IB and study protocol(s) also should clearly describe whether the comparator used in each study is the US-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature that clearly differentiates these products. If a non-U.S.-licensed comparator product is being used in a study conducted in the United States, the IB and study protocol(s) should clearly convey that the product is not FDA-approved and is considered an investigational new drug in the United States. The IB and study protocol(s) also should avoid conclusory statements regarding regulatory determinations (e.g., “comparable,” “biosimilar,” “interchangeable,” “highly similar”) that have not been made.

II. PROVISIONS RELATED TO REQUIREMENT TO SUBMIT A BLA FOR A “BIOLOGICAL PRODUCT”

Q. II.1. [This question and answer have been withdrawn and moved to FDA’s draft guidance for industry, New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2).]

Q. II.2. How is “product class” defined for purposes of determining whether an application for a biological product may be submitted under section 505 of the FD&C Act during the transition period? [Issued April 2015]

A. II.2. For purposes of section 7002(e)(2) of the Affordable Care Act, a proposed biological product will be considered to be in the same “product class” as a protein product previously approved under section 505 of the FD&C Act on or before March 23, 2010, if both products are homologous to the same gene-coded sequence (e.g., the INS gene for insulin and insulin glargine) with allowance for additional novel flanking sequences (including sequences from other genes). Products with discrete changes in gene-coded sequence or discrete changes in post-translational modifications may be in the same product class as the previously approved product even if the result may be a change in product pharmacokinetics.
For naturally derived protein products that do not have identified sequences linked to specific genes and that were approved under section 505 of the FD&C Act on or before March 23, 2010, a proposed biological product is in the same product class as the naturally derived protein product if both products share a primary biological activity (e.g., the 4-number Enzyme Commission code for enzyme activity).

However, for any protein product (whether naturally derived or otherwise), if the difference between the proposed product and the protein product previously approved under section 505 of the FD&C Act alters a biological target or effect, the products are not in the same product class for purposes of section 7002(e)(2) of the Affordable Care Act.

**Q. II.3. What type of marketing application should be submitted for a proposed antibody-drug conjugate?**

*Moved to Final from Draft December 2018*

A. II.3. A BLA should be submitted for a proposed monoclonal antibody that is linked to a drug (antibody-drug conjugate). FDA considers an antibody-drug conjugate to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857-49858 (August 25, 2005)).

CDER is the FDA center assigned to regulate antibody-drug conjugates, irrespective of whether the biological product constituent part or the drug constituent part is determined to have the primary mode of action. For more information see section 503(g) of the FD&C Act; see also, e.g., Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research (June 30, 2003), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm; Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (October 31, 1991), available at https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm.

To enhance regulatory clarity and promote consistency, CDER considered several factors to determine the appropriate marketing application type for antibody-drug conjugates, including the relative significance of the safety and effectiveness questions raised by the constituent parts, particularly the highly specific molecular targeting by the antibody to a cell type, cellular compartment, or other marker at the site of action (as distinguished from mere alteration of systemic pharmacokinetics).
In light of such factors, CDER considers submission of a BLA under section 351 of the PHS Act to provide the more appropriate application type for antibody-drug conjugates.

Sponsors seeking to submit a BLA for a proposed antibody-drug conjugate may contact CDER’s Office of New Drugs at 301-796-0700 for further information.

III. EXCLUSIVITY

Q. III.1. Can an applicant include in its 351(a) BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act? [Moved to Final from Draft December 2018]

A. III.1. Yes. An applicant may include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHS Act, and FDA will consider the applicant’s assertions regarding the eligibility of its proposed product for exclusivity. For more information, see FDA’s draft guidance for industry on Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act. The draft guidance describes the types of information that reference product sponsors should provide to facilitate FDA’s determination of the date of first licensure for their products.

Q. III.2. How can a prospective biosimilar applicant determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed? [Issued April 2015]

A. III.2. A searchable database for Orphan Designated and/or Approved Products and indications is available on FDA’s Web site, and is updated on a monthly basis (see https://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm). FDA will not approve a subsequent application for the “same drug” for the same indication during the 7-year period of orphan exclusivity, except as otherwise provided in the FD&C Act and 21 CFR part 316.

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16 This draft guidance, when finalized, will provide FDA’s current thinking on this topic.
APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

40th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

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The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2019.

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2020
therapeutically equivalent to the applicant’s drug product if the applicant’s drug product is rated either with an AB or three-character code or is single source in the Orange Book. Drugs coded as AB under a heading are considered therapeutically equivalent only to other drugs coded as AB under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

AN Solutions and powders for aerosolization

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in general-use delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded AN. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded BN, unless they have met an appropriate bioequivalence standard and are otherwise determined to be therapeutically equivalent. Solutions or suspensions in a specific delivery system will be coded AN if the bioequivalence standard is based upon in vitro methodology, if bioequivalence needs to be demonstrated by in vivo methodology then the drug products will be coded AB.

AO Injectable oil solutions

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, historically some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included in the Orange Book (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these
products are on the market without FDA approval and FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

Consistent with the definition of strength included in Section 1.2, Therapeutic Equivalence-Related Terms, the strength of parenteral drug products generally is identified by both the total drug content and the concentration of drug substance in a container approved by FDA.16 In the past, the strength of liquid parenteral drug products in the Orange Book has not been fully displayed. Rather, the strength of liquid parenteral drug products in the Orange Book has been displayed in terms of concentration, expressed as x mg/mL. Generally, the amount of dry powder or lyophilized powder in a container is identified as the strength, expressed as x mg/vial.

However, FDA subsequently realized that the format of the Orange Book with respect to parenteral solutions should be changed to reflect that each strength of a drug is considered to be a separate listed drug. The Orange Book displays the strength of all new approvals of parenteral solutions. Previously (i.e., prior to 2003), we would have displayed only the concentration of an approved parenteral solution, e.g. 50 mg/mL. For example, if this application had a 20 mL and 60 mL container approved, we would now display two product strengths, listing both total drug content and concentration of drug substance in the relevant approved container, e.g. 1 gm/20 mL (50 mg/mL) and 3 gm/60 mL (50 mg/mL).

**AT Topical products**

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays, suppositories, and inserts. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of in vivo bioequivalence has been granted, or the application contains adequate scientific evidence establishing through an in vitro approach the bioequivalence of the product to a selected reference product, and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded AT. Pharmaceutically equivalent topical products that raise questions of bioequivalence and for which a waiver of in vivo bioequivalence has not been granted, including all post-1962 non-solution topical drug products, are coded AB when supported by adequate in vivo bioequivalence data, and BT in the absence of such data.

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16 The strengths of certain parenteral drug products, including contrast agents, may be expressed as a percentage.
EXHIBIT 12
BRIEFING

7 Labeling. This general chapter provides definitions and standards for labeling of official articles. Note that, as with compendial quality standards, labeling requirements also may be enforceable under law. In the United States, to avoid being deemed misbranded, drugs recognized in USP–NF must be packaged and labeled in compliance with compendial standards [see the Food, Drug, and Cosmetic Act (FDCA) sections 501(b), 502(e)(3)(b), 502(g), and 21 Code of Federal Regulations 299.5]. FDCA also recognizes compendial (USP–NF) packing and labeling standards for “deteriorative drugs” [502(h)].

The Expert Committee proposes relocating all labeling requirements from the Preservation, Packaging, Storage, and Labeling section in the General Notices and general chapter Injections 1 to create this new chapter. The labeling standards for ferrules and cap overseals in this chapter have not changed and will become official on December 1, 2013. Many monographs have unique labeling requirements that should be used consistently.

(NSL: D. Bohannon.)
Correspondence Number—C106248

Comment deadline: March 31, 2012

Add the following:

LABELING

DEFINITION

The term labeling designates all labels and other written, printed, or graphic matter on an article's immediate container or on or in any package or wrapper in which it is enclosed, except any outer shipping container. The term label designates that part of the labeling on the immediate container.

A shipping container that contains a single article, unless the container also is essentially the immediate container or the outside of the consumer package, must be labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

In addition to compendial requirements, articles in USP–NF also are subject to compliance with more comprehensive labeling requirements promulgated by governmental bodies.

LABELS AND LABELING
The label states the following information:

- name of the preparation
- in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume
- in the case of a dry preparation, the amount of active ingredient
- the route of administration
- a statement of storage conditions and an expiration date
- the name and place of business of the manufacturer, packer, or distributor
- an identifying lot number.

The lot number must be traceable to the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

If the individual monograph permits varying concentrations of active ingredients in a large-volume parenteral (LVP), the concentration of each ingredient named in the official title is stated as if it were part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

If the complete formula is not specified in the individual monograph, the labeling includes the following information: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent must be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone if the formula is specified in the individual monograph], the amount that will be used to attain a specific concentration of active ingredient, the final volume of solution, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration or beyond-use date (see Expiration Date and Beyond-use Date below).

Containers for injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L should be labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections that are intended for veterinary use should be labeled to that effect.

The container shall be labeled so that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

**Amount of Ingredient per Dosage Unit**
The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts then are provided in the labeling.

Official articles in capsule, tablet, or other dosage forms shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each unit. An exception involves unit-dose oral solutions or suspensions (whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent). For these products the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in Deliverable Volume 698. Official drug products not in unit dosage form shall be labeled to show the quantity of each active ingredient in each milliliter or in each gram or to express the percentage of each such ingredient (see General Notices 8.140, Percentage Concentrations). Exceptions are oral liquids or solids intended to be constituted to yield oral liquids that, alternatively, can be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, declarations of strength or quantity shall be stated only in metric units. See also General Notices 5.50.10, Units of Potency (Biological).

Expiration Date and Beyond-use Date

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All products shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background, or it shall be sharply embossed and easily understood (e.g., “EXP 6/12,” “Exp. June 12,” or “Expires 6/12”). The monographs for some preparations state how the labeled expiration date shall be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the product, with the following exceptions: the label need not show an expiration date if the drug product or nutritional supplement is packaged in a container that is intended for sale without prescription, if the labeling states no dosage limitations, and if the product or supplement is stable for not less than 3 years when stored under the prescribed conditions.

If an official product is required to bear an expiration date, the product shall be dispensed solely in or from a container labeled with an expiration date, and the date on which the article
is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article can be expected to meet the requirements of the compendial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. If an expiration date is stated only in terms of the month and the year, then the intended expiration date is the last day of the stated month. The beyond-use date is the date after which a product shall not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer. The beyond-use date shall not be later than the expiration date on the manufacturer's container.

For articles that require constitution before use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining a beyond-use date the dispenser shall take into account, in addition to any other relevant factors:

- the nature of the drug
- the container in which it was packaged by the manufacturer and the expiration date thereon
- the characteristics of the patient's container, if the article is repackaged for dispensing
- the expected storage conditions to which the article may be exposed
- any unusual storage conditions to which the article may be exposed
- the expected length of the course of therapy.

After considering these factors, the dispenser shall label a container with a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph or in the absence of stability data to the contrary, the beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser shall maintain packaging and storage facilities at a mean kinetic temperature not greater than 25°C. The plastic material used in packaging the dosage forms shall afford better protection than polyvinyl chloride, which does not adequately protect against moisture permeation. Dispensers shall keep records of the temperature of the facility where the dosage forms are stored and of the plastic materials used in packaging.

STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS
For single- and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers that hold a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL.

The following formats are acceptable for contents of greater than 1 mL:

- total strength/total volume: 500 mg/10 mL
- strength/mL: 50 mg/mL
- or
- total strength/total volume: 25,000 Units/5 mL
- strength/mL: 5000 Units/mL.

The following format is acceptable for contents of less than 1 mL: 12.5 mg/0.625 mL.

There are some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be effective in preventing medication errors (e.g., insulin). Another example is the use of lidocaine or similar drugs for local anesthesia where the product is ordered and administered by percentage (e.g., 1% or 2%). In such cases, the total strength should be expressed: for example, 1% (100 mg/10 mL). Dry solids that must be reconstituted should follow the same format with the exception that only the total strength of the drug should be listed, not the strength/total volume or strength/mL.

**Use of Leading and Terminal Zeros**

To help minimize the possibility of errors in drug dispensing and administration, when the quantity of active ingredient is expressed in whole numbers it shall be shown without a decimal point followed by a terminal zero (e.g., express as 4 mg, not 4.0 mg). When the quantity of active ingredient is expressed as a decimal number smaller than 1, it shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg, not .2 mg).

**Labeling for Product Categories**

**Alcohol**

The alcohol content in a liquid preparation shall be stated on the label as a percentage (v/v) of C₂H₅OH.
Botanical Products

The label of a herb or other botanical intended for use as a dietary supplement shall bear the statement, “If you are pregnant or nursing a baby, seek the advice of a health professional before using this product”.

Compounded Preparations

The label on the container or package of an official compounded preparation shall bear a beyond-use date after which the compounded preparation should not be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned, in lieu of an expiration date, based on criteria that are different from those applied to manufactured drug products. The monograph for an official compounded preparation typically includes a specified beyond-use date. The beyond-use date states the time following the date of compounding during which the preparation, when properly stored, can be used. In the absence of stability information, beyond-use dating should be assigned as recommended in Chapter Pharmaceutical Compounding—Nonsterile Preparations 〈795〉. (See Stability Criteria and Beyond-use Dating in general chapter Pharmaceutical Compounding—Nonsterile Preparations 〈795〉, Stability of Compounded Preparations).

Electrolytes

The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Ferrules and Cap Overseals

Healthcare practitioners using injectable products must be able to easily see and act on labeling statements that convey important safety messages critical for the prevention of imminent life-threatening situations. These cautionary labeling statements must be simple, concise, and devoid of nonessential information. Products that do not require cautionary statements should be free of information, so that those with cautionary statements are immediately apparent. Accomplishing this requires a systematic approach to labeling of injectable products, and one that assures that the ferrule and cap overseal—an area of these products that is highly visible to practitioners as they use these medicines—is reserved for
critical safety messages. Accordingly:

1. Only cautionary statements may appear on the top (circle) surface of the ferrule and/or cap overseal of a vial containing an injectable product. The cautionary statement should appear on both the ferrule and cap but may appear solely on the ferrule if the cap overseal is transparent and the cautionary statement beneath the cap is readily legible. A cautionary statement is one intended to prevent an imminent life-threatening situation and may include instructional statements that provide potency or other safety-related instructions if warranted. Examples of such statements include but are not limited to: “Warning—Paralyzing Agent” and “Dilute before Using.” The cautionary statement should be printed in a contrasting color and clearly visible under ordinary conditions of use.

2. If no cautionary statement is necessary, the top surface of the vial, including the ferrule and cap overseal, must remain blank.

3. Other statements or features including but not limited to identifying numbers or letters, such as code numbers, lot numbers, company names, logos, or product names, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products but not on the top (circle) surface of the ferrule or cap overseal. The appearance of such statements or features on the skirt surface of the ferrule should not detract from, or interfere with, the cautionary statement on the top surface.

Official December 1, 2013

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: “Warning: Paralyzing Agent” or “Paralyzing Agent” (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Parenteral and Topical Preparations

The label of a preparation intended for parenteral or topical use shall state the names of all added substances (see General Notices 5.20., Added Substances, Excipients, and...
Ingredients) and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Aluminum in Large-volume Parenterals, Small-volume Parenterals, and Pharmacy Bulk Packages Used in Total Parenteral Nutrition Therapy

1. The aluminum content of large-volume parenterals (LVPs) used in total parenteral nutrition (TPN) therapy must not exceed 25 µg/L.

2. The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the Precautions section of the labeling of all LVPs used in TPN therapy.

3. If the maximum amount of aluminum in small-volume parenterals (SVPs) and pharmacy bulk packages (PBPs) is 25 µg/L or less, instead of stating the exact amount of aluminum that each contains, as in paragraph (4), the immediate container label for SVPs and PBPs used in the preparation of TPN parenterals (with exceptions as noted below) may state: “Contains no more than 25 µg/L of aluminum.” If the SVP or PBP is a lyophilized powder, the immediate container label may state the following: “When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L.”

4. The maximum level of aluminum at expiry must be stated on the immediate container label of all SVPs and PBPs used in the preparation of TPN parenteral and injectable emulsions. The aluminum content must be stated as follows: “Contains no more than ___ µg/L of aluminum.” The immediate container label of all SVPs and PBPs that are lyophilized powder used in the preparation of TPN solutions must contain the following statement: “When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than ___ µg/L.” This maximum amount of aluminum must be stated as the highest one of the following three levels:
   - The highest level for the batches produced during the past three years
   - The highest level for the latest five batches
   - The maximum level in terms of historical levels, but only until completion of production of the first five batches after 26 July 2004.

The package insert for all LVPs, SVPs, and PBPs used in the preparation of TPN products shall contain the following statement in the Warning section of the label:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature
neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products.

**Potassium Chloride for Injection Concentrate**

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampoule is prohibited, except for *Potassium Chloride for Injection Concentrate*.

**Salts of Drugs**

It is an established principle that official articles shall have only one official title (see separate compendial nomenclature requirements). For purposes of saving space on labels and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids, but these symbols are not used when the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not).

**Special Capsules and Tablets**

The label of any form of Capsule or Tablet intended for administration other than by swallowing intact shall bear a prominent indication of the manner in which it should be used.

**Products that Contain Vitamins**

The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E also may be stated in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.
Auxiliary Information - Please check for your question in the FAQs before contacting USP.