February 23, 2024

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Re: Docket No. FDA-2020-P-2247

Dear Ms. Denton:

This responds to your citizen petition received on December 2, 2020 (Petition), and submitted on behalf of Boehringer Ingelheim Pharmaceuticals, Inc. (BI).[1] Your Petition requests that the Food and Drug Administration (FDA or the Agency) interpret the term "strength" in section 351(k) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(k)) with respect to parenteral solutions "to mean the 'total drug content' in the relevant container (*e.g.*, single-dose vial, prefilled syringe) without regard to concentration or total volume" (Petition at 2). Your Petition also requests that FDA revise applicable Agency guidance documents to be consistent with this interpretation and "[a]pply 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)" (Petition at 2).

FDA has considered your Petition, and the comments and summary of a listening meeting submitted to the public docket established for this Petition. We note that there are comments[2] submitted to the public docket for the draft guidance for industry titled *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)* (September 2021)[3] that discuss issues related to this Petition.

For the reasons described in further detail in this response, your Petition is denied.

[1] On May 28, 2021, FDA issued an interim response to this Petition pursuant to 21 CFR 10.30(e)(2).

[2] See Docket No. FDA-2011-D-0611, available at Regulations.gov.

[3] This draft guidance, when final, will represent the FDA's current thinking on this topic.

I. BACKGROUND

A. Biologics Price Competition and Innovation Act of 2009

The Biologics Price Competition and Innovation Act of 2009 (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 reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Public Law 111–148)). Congress previously enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the "Hatch Waxman Amendments"), which, among other things, established abbreviated approval pathways for drug products in section 505(b)(2) and (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2) and (j)).

To provide context for the discussion of the Agency's interpretation of the term "strength" in the requirement that "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product" in section 351(k)(2)(A)(i)(IV) of the PHS Act (which applies to biosimilar and interchangeable biosimilar products), we begin with background on the Hatch-Waxman Amendments and the Agency's interpretation of the term "strength" in the requirement that "the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug" in section 505(j)(2)(A)(iii) of the FD&C Act (which applies to generic drug products). Your Petition focuses on "parenteral solutions" regulated as biological products. Although "parenteral solutions" is not a descriptor that generally is used in the context of biological products, we use the terms "parenteral solution" or "liquid parenteral drug product" in this response to refer to drug or biological products that are solutions intended solely for administration by injection (also referred to as an "injection" dosage form).

B. Hatch-Waxman Amendments to the FD&C Act

The Hatch-Waxman Amendments reflect Congress' efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[4] To obtain approval of a generic drug product, an applicant relies on FDA's finding of safety and effectiveness for a previously approved drug product (the reference listed drug (RLD)),[5] and must demonstrate, among other things, that the proposed generic drug product is the same as the RLD in certain ways.

Specifically, an abbreviated new drug application (ANDA) requesting approval of a proposed generic drug product must contain information to show that the proposed generic drug product is the same as the RLD with respect to active ingredient(s), conditions of use, and labeling (except for certain permissible labeling differences), and also must include "information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those

[4] See H. Rept. 98–857, part 1, at 14–15 (1984), reprinted in 1984 U.S. Code Congressional and Administrative News 2647 at 2647–2648.

[5] The RLD is "the listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)).

of the listed drug" (section 505(j)(2)(A) of the FD&C Act). In addition, an ANDA applicant must demonstrate that its proposed product is bioequivalent to the RLD (see section 505(j)(2)(A)(iv) of the FD&C Act). An applicant that can meet the requirements for approval under section 505(j) of the FD&C Act may rely upon the Agency's finding of safety and effectiveness for the RLD and need not independently demonstrate the safety and effectiveness of its proposed product, as would be required for approval of a "stand-alone" new drug application (NDA).

The requirement for a proposed generic drug product to have the same "strength" as the RLD reflects, among other things, that different strengths of a drug product are regarded as different drug products and therefore are different listed drugs.[6] FDA defines the term "strength" in the context of section 505(j)(2)(A)(iii) of the FD&C Act to mean:

> [T]he amount of drug substance contained in, delivered, or deliverable from a drug product, which includes:
> (1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable.
> (ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or
> (2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).[7]

The weights and measures used to determine the "strength" of a drug product may differ based on the type of drug product or dosage form.[8] For liquid parenteral drug products in an "injection" dosage form (e.g., a solution), FDA has a longstanding history of considering a difference in either the total quantity of drug substance (e.g., milligram (mg)) or the concentration (e.g., mg per milliliter (mL)) to be a difference in the "strength" of the product for purposes of section

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[6] See Apotex, Inc. v. Shalala, 53 F. Supp. 2d 454 (D.D.C.), *aff'd*, 1999 U.S. App. LEXIS 29571 (D.C. Cir. 1999); see also "Abbreviated New Drug Application Regulations"; final rule, 57 FR 17950, 17954 (April 28, 1992) ("In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug."); and "Abbreviated New Drug Applications and 505(b)(2) Applications"; final rule, 81 FR 69580, 69618 (October 6, 2016) ("confirm[ing] that different strengths of an approved drug product continue to be regarded as different listed drugs").

[7] 21 CFR 314.3(b); see also "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6809 and 6816, February 6, 2015) (proposing to "codify FDA's interpretation of the term 'strength' in the context of section 505(j)(2)(A)(iii) of the FD&C Act" and stating that certain definitions, including "strength," are "intended to codify our longstanding use of these terms, rather than substantively change the meaning") and § 210.3(b)(16) (21 CFR 210.3(b)(16)).

[8] See "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816, February 6, 2015).

505(j)(2)(A)(iii) of the FD&C Act.[9] The Agency has explained that differences in either the concentration or the total drug content of a liquid parenteral drug product can introduce risks for medication errors and incorrect dosing of patients that may need to be evaluated on a product-specific basis and defining strength to include both concentration and total drug content mitigates these risks.[10]

An applicant may submit a suitability petition to FDA requesting permission to submit an ANDA (a "petitioned ANDA") for a generic drug product that differs from a listed drug in strength (or dosage form, route of administration, or active ingredient (in a product with more than one active ingredient)).[11] FDA will grant a suitability petition unless the Agency determines that investigations must be conducted to show the safety and effectiveness of the proposed change from the listed drug.[12] A generic drug product approved in a "petitioned ANDA" under section 505(j)(2)(C) of the FD&C Act is not pharmaceutically equivalent[13] or therapeutically equivalent[14] to the RLD, and therefore is not assigned a therapeutic equivalence code with respect to its RLD in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book). In implementing this provision, FDA has considered proposed changes only in the concentration (as well as proposed changes only in the total quantity of drug substance or in both the concentration and the total drug content) of a liquid parenteral drug product to be petitionable changes that do not result in a therapeutically equivalent drug product.

The Orange Book[15] identifies drug products that have been approved under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, and for which the product has not been discontinued from marketing (or approval of the application has not been withdrawn) for what FDA has determined are reasons of safety or effectiveness. Among other things, the Orange Book provides FDA's therapeutic equivalence evaluation for

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[9] See, e.g., "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816 (February 6, 2015); see also section II.A of this response.

[10] See, e.g., "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816 (February 6, 2015); see also section II.A of this response.

[11] See section 505(j)(2)(C) of the FD&C Act; see also § 314.93 (21 CFR 314.93).

[12] See section 505(j)(2)(A), (C) of the FD&C Act and § 314.93(e)(1)(i).

[13] See § 314.3(b) (21 CFR 314.3(b)) ("*Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.").

[14] See § 314.3(b) ("*Therapeutic equivalents* are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."). The Preface to the Orange Book explains that "FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product can be expected to have the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling." Orange Book, 43rd ed. (2023), at viii.

[15] See generally section 505(j)(7) of the FD&C Act.

multisource prescription drug products approved under section 505 of the FD&C Act, identifies listed drugs that have been designated as RLDs, lists patent information submitted by NDA holders pursuant to section 505(c)(2) of the FD&C Act, identifies drug products that have qualified for periods of exclusivity under the FD&C Act, and lists the strength of each listed drug.

C. Biosimilar and Interchangeable Biosimilar Products

Section 351(k) of the PHS Act, added by the BPCI Act, sets forth the requirements for the licensure of a biosimilar or interchangeable biosimilar product. Biosimilarity is defined by statute 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."[16] A 351(k) BLA must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, an assessment of toxicity, and a clinical study or studies (see section 351(k)(2)(A)(i)(I) of the PHS Act), unless FDA has determined that an element described in section 351(k)(2)(A)(i)(I) of the PHS Act is unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act). A 351(k) BLA also is required to include information demonstrating, among other things, that "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)(IV) of the PHS Act). Although section 505(j) of the FD&C Act also requires an ANDA to have the same route of administration, dosage form, and strength as its listed drug, section 505(j) of the FD&C Act allows for the possibility of certain differences (e.g., in strength) through submission of a petitioned ANDA. Congress did not provide a statutory pathway under section 351(k) of the PHS Act for an applicant to petition to seek licensure of a proposed biosimilar that differs from the reference product in strength (or dosage form or route of administration).

To meet the standard for "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity to the reference product 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 biosimilar products may be substituted for the reference product without the intervention of the prescribing health care provider (section 351(i)(3) of the PHS Act).

Since 2012, FDA guidance has explained that, in general, an applicant can demonstrate that its proposed biosimilar or interchangeable biosimilar product with an "injection" dosage form (e.g., a parenteral solution) 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

[16] See section 351(i)(2) of the PHS Act; see also section 351(i)(4) of the PHS Act (defining "reference product" to mean "the single biological product licensed under [section 351(a)] against which a biological product is evaluated in an application submitted under [section 351(k)]").

concentration of drug substance (in mass or units of activity per unit volume).[17] FDA guidance also explains that, "[a]s a scientific matter, there may be a need to take into account different factors and approaches in determining the strength of different biological products."[18] For example, the strength of a vaccine in an injection or injectable suspension dosage form is generally described as a specified volume (e.g., 0.5 mL) for a single dose because effectiveness of a vaccine is based on the immune response to a dose, either alone or as a series, and the immune response elicited by a vaccine depends on the particular antigen, how it is presented, and other factors (e.g., presence of an adjuvant) and not only the quantity of a particular antigen. Moreover, the antigen content is often expressed in units that may differ between vaccines containing the same antigen(s),[19] and even if the antigen content were presented in the same unitage for different vaccines, it may not be meaningful to prescribing decisions because effectiveness is not based only on the quantity of a particular antigen. For purposes of this response, we focus on therapeutic biological products regulated by CDER.

FDA considers an "injection" (e.g., a parenteral solution) to be a different dosage form from "for injection" (which describes a dry solid, such as a lyophilized powder, from which a constituted or reconstituted solution is prepared for injection).[20] Although FDA guidance initially recommended that an applicant can demonstrate that its proposed biosimilar or interchangeable biosimilar product with a "for injection" dosage form has the same strength as the reference product using the same criteria used for an injection dosage form, FDA modified its recommendations in 2018 because this approach did not align with the Agency's interpretation of "strength" for generic drug products with a "for injection" dosage form. Accordingly, the

[17] See FDA Draft Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (February 2012) at Q&A I.12; FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015) at Q&A I.12; FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)" (December 2018) at Q&A I.12, and FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)" (September 2021) at Q&A I.12. We note that BI submitted comments to the public docket for the draft guidance on April 13, 2012, but BI did not comment on FDA's interpretation of "strength" (see Docket No. FDA-2011-D-0611-0017).

[18] See, e.g., FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)" (September 2021) at Q&A I.12.

[19] See, e.g., approved product labeling for Havrix (Hepatitis A Vaccine) injectable suspension and Vaqta (Hepatitis A Vaccine, Inactivated) suspension for injection, available at https://www.fda.gov/vaccines-blood-biologics/vaccines/havrix and https://www.fda.gov/vaccines-blood-biologics/vaccines/vaqta. The content of Hepatitis A virus antigen is expressed in different units for Havrix and Vaqta. However, both vaccines are available in the same strength as 0.5 mL single-dose and 1 mL single-dose presentations.

[20] See FDA Guidance for Industry, "Questions and Answers on Biosimilar Development and the BPCI Act" (Rev. 2, September 2021) at Q&A I.18; see also Letter dated October 24, 2007, from Janet Woodcock, M.D., Acting Director, CDER, to AAC Consulting Group/Kendle regarding Eloxatin (oxaliplatin for injection), 50 and 100 mg/vial (Docket No. FDA-2006-P-0006, formerly 2006P-0298) (Eloxatin Petition Response) (explaining that "[t]he Eloxatin powder formulation would be considered to be a different dosage form than the Eloxatin aqueous solution because injectable drug powders and injectable solutions are different dosage forms" and referring to the concentration (5 mg/mL) of the aqueous solution approved in 2005).

Q&A on "strength" that previously had been included in a final guidance[21] was withdrawn because the Agency determined that the Q&A should be revised with respect to the demonstration of same "strength" for proposed biosimilar and interchangeable biosimilar products with a "for injection" dosage form. In the revised draft Q&A guidance issued in 2018, FDA recommended that for dry solids, same "strength" can be shown by demonstrating that both products have the same total content of drug substance (in mass or units of activity).[22] FDA further explained that, although not a part of demonstrating same "strength," the 351(k) BLA "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."[23]

Despite this modification to the interpretation regarding demonstrating the same "strength" for proposed biosimilar and interchangeable biosimilar products with a "for injection" dosage form, FDA guidances from February 2012 through the current revised draft guidance issued in September 2021 have consistently described FDA's expectation that a proposed biosimilar product with an "injection" dosage form (e.g., a parenteral solution) demonstrate same strength as the reference product by showing 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).

D. Adalimumab Products

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor. On December 31, 2002, FDA licensed BLA 125057 submitted by Abbott Laboratories for Humira (adalimumab) injection, 40 mg/0.8 mL (50 mg/mL) (informally described as *Original Concentration Humira* in this response), with an indication for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. FDA subsequently licensed Humira for other uses and strengths.[24]

On November 23, 2015, AbbVie, Inc. (the current holder of BLA 125057) obtained licensure of Humira injection, 40 mg/0.4 mL (100 mg/mL), in a single-dose prefilled syringe that differed from the previously licensed Humira in excipients and concentration (informally described as *High Concentration Humira* in this response).[25] To support licensure of High Concentration

[21] See FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015) at Q&A I.12, which has been superseded by subsequent guidance.

[22] FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)" (December 2018) at Q&A I.12.

[23] *Id.*

[24] See Humira (adalimumab) injection labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125057s417lbl.pdf.

[25] See Humira (adalimumab) injection labeling, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125057s394lbl.pdf

Humira, AbbVie, Inc., primarily relied on pharmacokinetic (PK) data that evaluated the bioavailability of the proposed 100 mg/mL formulation compared to the approved 50 mg/mL formulation in healthy volunteers and the established safety and efficacy profile for the currently approved 50 mg/mL formulation.[26] AbbVie, Inc. subsequently obtained licensure of High Concentration Humira in 40 mg/0.4 mL and 80 mg/0.8 mL strengths in a single-dose prefilled pen presentation and in 10 mg/0.1 mL, 20 mg/0.2 mL, and 80 mg/0.8 mL strengths in a single-dose prefilled syringe presentation.

On September 23, 2016, FDA licensed Amjevita (adalimumab-atto) injection, 20 mg/0.4 mL and 40 mg/0.8 mL, the first biosimilar to the Original Concentration Humira (adalimumab) injection, 20 mg/0.4 mL and 40 mg/0.8 mL. FDA subsequently licensed additional biosimilar or interchangeable biosimilar products to certain Original Concentration Humira and High Concentration Humira products (the following table is current as of February 20, 2023):

BLA Number	Product	Approved Strengths	
		Same Strength as Original Concentration Humira	Same Strength as High Concentration Humira
BLA 761118	Abrilada (adalimumab-afzb) injection	10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	—
BLA 761024	Amjevita (adalimumab-atto) injection	10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	20 mg/0.2 mL 40 mg/0.4 mL 80 mg/0.8 mL
BLA 761058	Cyltezo (adalimumab-adbm) injection	10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	—
BLA 761059	Hadlima (adalimumab-bwwd) injection	40 mg/0.8 mL	40 mg/0.4 mL
BLA 761154	Hulio (adalimumab-fkjp) injection	20 mg/0.4 mL 40 mg/0.8 mL	—
BLA 761071	Hyrimoz (adalimumab-adaz) injection	10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	10 mg/0.1 mL 20 mg/0.2 mL 40 mg/0.4 mL 80 mg/0.8 mL
BLA 761255	Idacio (adalimumab-aacf) injection	40 mg/0.8 mL	—
BLA 761219	Yuflyma (adalimumab-aaty) injection	—	20 mg/0.2 mL 40 mg/0.4 mL 80 mg/0.8 mL
BLA 761216	Yusimry (adalimumab-aqvh) injection	40 mg/0.8 mL	—

[26] See BLA 125057, Supplement 394, Summary Review for Regulatory Action, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125057Orig1s394SumR.pdf.

The above-referenced products have been demonstrated to be biosimilar to or interchangeable with Humira (adalimumab) injection for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in their product labeling.[27]

BI's request focuses on products, such as its Cyltezo (adalimumab-adbm) injection, that contain the same total content of drug substance but differ in concentration from a biological product licensed under section 351(a) of the PHS Act. BI seeks a revised interpretation of "strength" that would allow its Cyltezo (adalimumab-adbm) injection, which contains the same total content of drug substance and same concentration as Original Concentration Humira (e.g., 40 mg/0.8 mL), to be biosimilar to or interchangeable with High Concentration Humira (e.g., 40 mg/0.4 mL) in addition to Original Concentration Humira (see Petition at 6 and 19).[28]

II. DISCUSSION

A. When the BPCI Act Was Passed, FDA Interpreted "Strength" Under Section 505(j) of the FD&C Act To Require That a Generic Liquid Parenteral Drug Product Have the Same Total Content of Drug Substance and the Same Concentration As That of Its RLD

BI asserts that "[w]hen 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" (Petition at 9). BI maintains that "[a]lthough the term was not explicitly defined in either the statute or FDA's implementing regulations, FDA defined the term precisely" in FDA's Orange Book with respect to liquid parenteral drug products, which is the form in which most biological products historically have been approved (see Petition at 9-10). BI contends that "[t]he Orange Book is a highly relevant source for ascertaining FDA's definition of 'strength' for purposes of the Hatch-Waxman Act" because the Orange Book satisfies the requirement for "the list" described in section 505(j)(7)(A) of the FD&C Act (see Petition at 10). BI states:

> 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 drug products in the Orange Book have not been displayed[,]" only the

[27] For additional product information, including information on products that have been determined to be interchangeable with Humira, see FDA's Purple Book: Database of Licensed Biological Products, available at https://purplebooksearch.fda.gov.

[28] Although the Petition focuses on adalimumab products, BI's proposed approach also would have implications for other biological products such as Neupogen (filgrastim) injection (available in a 300 micrograms (mcg)/mL single-dose vial and a 300 mcg/0.5 mL single-dose prefilled syringe as well as a 480 mcg/1.6 mL single-dose vial and a 480 mcg/0.8 mL single-dose prefilled syringe) and Epogen/Procrit (epoetin alfa) injection (available in 20,000 Units/2 mL and 20,000 Units/mL multidose vials).

> 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.[29]

BI also asserts that "[t]he 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" (Petition at 11). BI contends that "[b]y 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" (Petition at 11).

FDA Response:

FDA disagrees with BI's assertion that the Agency interpreted the "strength" of a liquid parenteral drug product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act to mean only the total drug content at the time that the BPCI Act was passed. FDA's revisions to the Orange Book in 2003 aligned the display of strength information in the Orange Book with FDA's longstanding interpretation of strength for liquid parenteral drug products to include both the total drug content and the concentration of the drug product. These revisions to the Orange Book thus clearly distinguished between liquid parenteral drug products of different strengths (i.e., concentration and total drug content), which are considered different listed drugs.

In the preamble to FDA's proposed rule to implement portions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, FDA described its longstanding history of considering a difference in the total quantity of drug substance of a [liquid] parenteral drug product (e.g., a single- or multiple-dose vial) or a difference in the concentration of a [liquid] parenteral drug product to be a difference in the "strength" of the product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act.[30] Moreover, FDA's interpretation of "strength" as applied to liquid parenteral drug products is reflected in nearly forty years of implementation of the statutory requirement that an ANDA contain information to show, among other things, that the "strength" of the proposed generic drug product is the same as that of the RLD or, if the strength is different, the ANDA is filed pursuant to the approval of a suitability petition (see section 505(j)(2)(A)(iii) of the FD&C Act). The Agency has explained:

> Changes in strength for injections can be characterized either by a change in the total amount of drug in the container or a change in the concentration of the drug product. Either change can raise issues of safety or effectiveness for an injection. The Agency believes that it is in the best interest of public health to evaluate these changes prior to the

[29] Petition at 11.

[30] "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816 (February 6, 2015).

> submission of an [abbreviated new drug] application.[31]

Safety considerations arise from the concern that, because of the way parenteral drug products are prepared and administered, differences in either the concentration or the total drug content of a parenteral drug product can introduce risks for medication errors, including incorrect dosing of patients, that may need to be evaluated on a product-specific basis.[32] Drug delivery through parenteral administration generally is fast, efficient, and precise. For intravenous routes of administration in particular, the drug is distributed almost immediately and physiological responses to the drug follow rapidly. Once a drug is injected intravenously, there is generally no way to reverse the drug's effects or remove it from the body.

In certain cases, a difference between the concentration of the RLD and a generic drug product, for example – even if total drug content has not changed – may lead to end-user confusion that could result in dosing errors. There may be distinct risks of end-user confusion based on the administration context (e.g., healthcare professional versus patient or caregiver, emergency versus non-emergency situations, whether further dilution before administration is needed, intravenous infusion versus immediate injection). For example, the end user may need to use the concentration to calculate the volume necessary to prepare or administer a full dose or partial dose from a vial or a prefilled syringe. If the concentration is different between a generic drug product and its RLD, lay users, including patients and caregivers in particular, may have difficulty calculating correct volumes for dosing of the generic drug product. There also could be a risk of confusion for healthcare professionals in clinical settings if the total drug content remained the same, but the concentration changed. For example, a healthcare professional who is accustomed to using the RLD may not realize that another product was substituted for the RLD product that may require a different volume of product to be administered. In this case, due to negative transfer, it is foreseeable that end users could withdraw the same volume that they are accustomed to withdrawing with the RLD, without regard to the change in concentration, resulting in dosing errors.

FDA acknowledges that there also may be scenarios in which differences in concentration may have little to no impact on usability. For example, for drug products that are generally administered with an autoinjector or prefilled syringe, where the entire content is administered, the total drug content is the same, and the product is not labeled for dosing of less than the entire content or for multiple doses, different concentrations may not affect safety, effectiveness, or directions for use. However, FDA's definition of strength for liquid parenteral drug products accounts for its use in all scenarios, not just in the lowest risk scenarios described in this paragraph.

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[31] Letter dated June 19, 2012, from Keith O. Webber, Ph.D., Deputy Director, CDER/Office of Pharmaceutical Science, to Olsson, Frank and Weeda, P.C. (Docket No. FDA-2004-P-0418; formerly 2004P-0544) at 1, note 1 (denying suitability petition requesting permission to submit an ANDA for ondansetron hydrochloride (HCl) injection, 8 mg/4 mL in a prefilled syringe that relied on Zofran (ondansetron HCl) injection, 4 mg/2 mL vial). This docket number (and certain other docket numbers in subsequent references) were changed as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008, and we have provided the legacy docket number after the current docket number throughout, where applicable.

[32] "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816 (February 6, 2015).

It should be noted that even if there is mitigation of the risk of dosing and administration errors that can impact safety and effectiveness in certain scenarios where the entire content of the container closure is administered in a single dose, differences in drug substance concentration also can affect the quality profile of a drug product. For example, certain drug products may be more susceptible to chemical modifications (e.g., oxidation) or incompatibility with a container or with an excipient depending on concentration.[33]

Thus, the Agency's longstanding interpretation of the "strength" of a liquid parenteral drug product to include both the total drug content and the concentration of the drug product is scientifically justified and provides a consistent and predictable approach for the development and approval of generic drug products. Accordingly, the Agency has required submission of suitability petitions requesting permission to submit an ANDA for a strength that differs from the RLD where the applicant proposed only to change the concentration,[34] only to change the total quantity of drug substance,[35] or to change both the concentration and the total drug content[36] of a proposed generic drug product in an injection dosage form. The suitability petition process enables the Agency to evaluate proposed changes in strength (and certain other changes specified in section 505(j)(2)(C) of the FD&C Act) on a product-specific basis.

In 1992, for example, FDA granted a suitability petition that requested permission to file an ANDA for nalbuphine HCl injection, 20 mg/2 mL, which differed from the RLD (Nubain

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[33] See Hipper E, Lehmann F, Kaiser W, et Al. "Protein photodegradation in the visible range? Insights into protein photooxidation with respect to protein concentration." Int J Pharm X 2022; 5: 100155 (noting that "[p]rotein degradation scales with protein concentration").

[34] See, e.g., Letter dated August 1, 2001, from Gary J. Buehler, Director, CDER/ Office of Generic Drugs (OGD), to Lipomed, Inc. (Docket No. FDA-2000-P-0923, formerly 00P-1621) (denying suitability petition requesting permission to submit an ANDA for cladribine injection, 2 mg/mL in 5 mL vials, that relied on Leustatin (cladribine) injection, 1 mg/mL in 10 mL vials) (Cladribine Suitability Petition Response); Letter dated April 30, 2001, from Gary J. Buehler, Acting Director, CDER/OGD, to Gensia Sicor Pharmaceuticals, Inc. (Docket No. FDA-2000-P-1219, formerly 00P-1471) (denying suitability petition requesting permission to submit an ANDA for propofol injectable emulsion 2% in 200 mg/10 mL and 1000 mg/50 mL single-use vials that relied on Diprivan (propofol injectable emulsion 1%) 200 mg/20 mL single-use ampoules and 1000 mg/100 mL single-use vials, despite the applicant's contention that the "new concentration will provide the practitioner with a wider range of dosing flexibility," especially for certain patients) (see Propofol Suitability Petition at 2 and Propofol Suitability Petition Response at 1). In the Propofol Suitability Petition Response, the Agency explained that the "request involves a change in strength from that of the listed drug product (i.e., from 10 mg/mL to 20 mg/mL)" and determined that the "proposed change in strength raise[d] questions of safety and effectiveness, and concluded that clinical trials are required for this specific drug product" (Propofol Suitability Petition Response at 1). See also Nalbuphine HCl Suitability Response and Dihydroergotamine Mesylate Suitability Petition Response, discussed *infra*.

[35] See, e.g., Letter dated August 18, 2006, from Gary J. Buehler, Director, CDER/OGD, to Ben Venue Laboratories, Inc. (Docket No. FDA-2004-P-0217, formerly 2004P-0434) (granting suitability petition requesting permission to submit an ANDA for fluconazole in sodium chloride 0.9% injection, 100 mg/50 mL, that relied on Diflucan (fluconazole) in sodium chloride 0.9% injection, 200 mg/100 mL).

[36] See, e.g., Letter dated February 8, 2021, from William H. Chong, Associate Director of Clinical Affairs, CDER/OGD to Gordon Johnston Regulatory Consultants, LLC (Docket No. FDA-2012-P-1251) (granting suitability petition requesting permission to submit an ANDA for morphine sulfate injection, 5 mg/mL, that relied on morphine sulfate injection, 4 mg/mL, finding that the proposed change in strength does not pose questions of safety or effectiveness).

[nalbuphine HCl] injection, 20 mg/mL) only in concentration. FDA explained that "[y]our request involves a change in strength (concentration) from that of the listed drug product (i.e., from 20 mg/mL to 10 mg/mL). The type of change you request is the type of change authorized under Section 505(j)(2)(c) of the Act."[37] The Agency made a finding that "the change in strength (concentration) for the specific proposed product does not pose questions of safety or effectiveness…" (*Id.* at 1). At that time, FDA's Orange Book listed the "strength" of liquid parenteral drug products by concentration without displaying the complete strength information (i.e., concentration and total drug content).[38] This approach to listing liquid parenteral drug products in the Orange Book did not align with FDA's longstanding practice of considering liquid parenteral drug products with the same concentration but different total drug content to have different strengths and therefore to be considered different drug products.

In the late 1990s, changes in eligibility for 180-day exclusivity[39] and applicants seeking to be eligible for a period of 180-day exclusivity for generic drug products of different strengths resulted in a reevaluation of the display of the strength of parenteral drug products in the Orange Book. [40] The absence of separate listed drug entries in the Orange Book for parenteral drug products of different strengths (based on both concentration and total drug content) led to difficulty in determining eligibility for 180-day exclusivity for generic drug products that referred to such RLDs. Accordingly, beginning in 2003, the Orange Book displayed the strength of parenteral drug products as both the concentration and the total drug content. In the 2003 edition of the Orange Book, FDA stated:

> 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. 50 mg/ml. **If this drug product had a 20 ml and 60 ml container approved the two products would be shown as 1 Gm [gram]/ 20 ml (50 mg/ml) and 3 Gm /60 ml (50 mg/ml).**[41]

The example highlighted in bold type above illustrates that FDA considers both the total drug content (e.g., 1 gm) and the concentration of the drug product (e.g., 1 gm/20 mL or 50 mg/mL) in

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[37] Letter dated September 11, 1992, from Roger L. Williams, M.D., Director, CDER/OGD, to Sterling Winthrop Inc. (Docket No. FDA-1992-P-0380-0004; formerly 92P-0224) at 1.

[38] See, e.g., Orange Book, 12th ed. (1992), at 3-199, see also 21 CFR 20.117(a)(3) (describing the public availability of a list of specified NDAs and ANDAs that includes, among other things, the "strength or potency of the product").

[39] See, e.g., Guidance on 180-day Generic Drug Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (June 1998).

[40] See supplement dated March 31, 2000, to citizen petition submitted by Hyman, Phelps & McNamara, P.C., requesting, among other things, "clarification that different multiple-dose container sizes [i.e., different total drug content] of parenteral drugs [that do not differ in the amount of active ingredient in a given volume of the drug – i.e., same concentration] are not different 'strengths' for purposes of 180-day Waxman-Hatch generic drug exclusivity" (Docket No. FDA-1999-P-0151, formerly 99P-4932). The citizen petition subsequently was withdrawn on June 28, 2000 (see Docket No. FDA-1999-P-0151-0005).

[41] Orange Book, 23rd ed. (2003), at xvii (emphasis added).

defining the strength of a liquid parenteral drug product. In focusing on the change from the previous listing practice to include the total drug content with the concentration for complete strength information, FDA (inartfully) explained: "The strength of parenteral drug 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 x mg/ml."[42] The 2003 update to the display of the strength of liquid parenteral drug products in the Orange Book did not reflect a change in FDA's interpretation of strength—concentration and total drug content continued to be assessed in determining the strength of liquid parenteral drug products. Notwithstanding the fact that certain Orange Book listings have not been updated to conform with the current display format of total drug content and concentration as the strength of liquid parenteral drug products,[43] FDA continues to assess both concentration and total drug content in determining each individually approved "strength" of a liquid parenteral drug product, consistent with FDA's longstanding practice. To that end, in 2016, the Orange Book was revised for clarity to state:

> 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.[3] 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 xmg/mL. The amount of dry powder or freeze dried powder in a container has always been identified as the strength, expressed as xmg/vial.
>
> With the finalization of the 1984 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 Orange Book now displays 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, we would now display two product strengths for this product, listing both total drug content and concentration of drug substance in the relevant approved container, e.g. 1Gm / 20mL (50mg/mL) and 3Gm / 60mL (50mg/mL).[44]

Although there are relatively few examples of applicants seeking to develop liquid parenteral drug products that contain the same total content of drug substance and differ only in concentration, the Agency has consistently regulated such products as different "strengths" under section 505(j)(2)(A)(iii) of the FD&C Act for more than 30 years—both before and after the change in the display of strength in the Orange Book in 2003. For example:

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[42] Orange Book, 23rd ed. (2003), at xvii.

[43] FDA has explained that "[t]o the extent that conventions for describing product identification information (i.e., active ingredients, dosage forms, routes of administration, product names, applicants, strengths) evolve over time, the Agency generally does not intend to revise such information for drug products already listed in the Orange Book, but rather intends to apply the change prospectively to drug products as they are added to the Orange Book." Orange Book, 43rd ed. (2023), at xxv.

[44] Orange Book, 36th ed. (2016), at xvi-xvii. Footnote 3 in the quoted excerpt states: "The strengths of certain parenteral drug products, including contrast agents, may be expressed as a percentage."

- In 2001, FDA denied a suitability petition requesting permission to submit an ANDA for cladribine injection in a strength (2 mg/mL in 5 mL vials) that differed from the RLD (1 mg/mL in 10 mL vials) only in concentration, even though the proposed product contained the same total quantity of drug substance (10 mg) as the RLD. The Agency determined that the "proposed change in strength (concentration) raises questions of safety and effectiveness. During normal use, Cladribine is administered at doses that are often associated with severe hematologic toxicity. A doubling of the dose, which may occur if the Agency permitted the approval of a more concentrated product, could result in serious and perhaps lethal toxicity …"[45]

- In 2005, FDA denied a suitability petition for dihydroergotamine mesylate injection that requested "a change in strength (concentration) from that of the listed drug product, i.e., from 1 mg/mL, 1 mL ampuls [sic] to 2 mg/mL, 0.5 mL pre-filled syringes. The total drug content for both products remains the same (i.e., 1 mg)."[46] The Agency stated that "[t]he change in strength (concentration) that you request is the type of change that is authorized under Section 505(j)(2)(C) of the Act." In its response to the suitability petition, FDA explained: "Dihydroergotamine is a vasoconstrictor and changes in concentration may induce changes in both local tolerability and in pharmacokinetics due to modified absorption of the drug product. Therefore, FDA is denying the petition under Section 505(j)(2)(C)(i) because investigations are necessary to show the safety and effectiveness of the proposed drug product because of the differing concentration."[47]

These examples illustrate a few of the scientific considerations described earlier in this section that informed the Agency's interpretation of the statutory term "strength" in the context of liquid parenteral drug products.

On January 11, 2007, FDA held a public workshop involving representatives from the Institute for Safe Medicine Practices and USP to explore how labels on intravenous drug products could be designed to minimize medication errors, including "placement, style and type of information, the need for standard expression of strength, quantity of information, and use of color on the label."[48] At that time, the expression of strength on liquid parenteral drug product labels differed depending on the package type and total volume.[49] For example, single-dose liquid parenteral drug products presented the strength as total quantity/total volume (e.g., 20 mg/4 mL) and

[45] See Cladribine Suitability Petition Response (Docket No. FDA-2000-P-0923) ("Therefore, FDA is denying the petition under Section 505(j)(2)(C)(i) because investigations are necessary to show the safety and effectiveness of the proposed drug product.").

[46] See Letter dated April 1, 2005, from Gary J. Buehler, Director, CDER/OGD, to Hyman, Phelps & McNamara, P.C. (Docket No. FDA-2003-P-0347, formerly 2003P-0556) at 1 (Dihydroergotamine Mesylate Suitability Petition Response).

[47] Dihydroergotamine Mesylate Suitability Petition Response (Docket No. FDA-2003-P-0347) at 1.

[48] See "Improving Patient Safety by Enhancing the Container Labeling for Parenteral Infusion Drug Products; Public Meeting"; Notice of Public Meeting and Request for Comments, 71 FR 68819 (November 28, 2006) (Docket No. FDA-2006-N-0104) (Parenteral Infusion Drug Product Public Meeting).

[49] See FDA Guidance for Industry, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" (May 2022) at 15.

multiple-dose liquid parenteral drug products presented the strength in terms of quantity/mL (e.g., 5 mg/mL) with the total volume (e.g., 4 mL) appearing separately on the label. For multiple-dose liquid parenteral drug products, there were medication errors due to healthcare providers misinterpreting quantity per mL (e.g., 5 mg/mL) to represent a total drug content and administering the entire contents of a container when only a portion of the total volume was needed.

USP subsequently revised USP General Chapter <1> (currently USP General Chapter <7>) to provide a consistent, standard approach to labeling liquid parenteral drug products (which USP discusses under the category of "injectable" drug products) regardless of package type (e.g., single-dose or multiple-dose).[50] For "small-volume injection" products, which constitute the majority of biological products, the USP general requirements for product labels were revised to consistently display the product strength as the quantity per total volume (i.e., total drug content) followed by the quantity per mL (i.e., concentration), which is expected to help reduce medication errors.[51]

FDA's view is that the different components of strength each provide important information to the end-user. The total drug content per total volume of drug product informs the end-user of the total amount of drug the container can deliver. The concentration (quantity per mL) is useful for performing calculations when preparing injectable products (e.g., weight- or body surface area-based dosing, administering less than the full content of the container). Accordingly, we disagree with BI's contention that revisions to the USP General Chapter to clearly express strength on the product label in terms of the "strength per total volume" followed by the "strength per mL" support BI's interpretation of the strength of a liquid parenteral drug product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act as only the total drug content.

Thus, when the BPCI Act was passed by Congress in 2009 and signed into law on March 23, 2010, the statutory term "strength" in section 505(j)(2)(A)(iii) of the FD&C Act had an existing, well-established administrative meaning that reflected both the total drug content (e.g., mg) and the concentration (e.g., mg/mL) for liquid parenteral drug products.

B. When the BPCI Act Was Passed, the Terms "Strength" and "Concentration" Had Overlapping Meanings

BI asserts that "'strength' and 'concentration' had distinct, non-overlapping meanings when the [BPCI Act] was enacted" (Petition at 12). BI further asserts that this purported distinction is

[50] See USP General Chapter <1> (Injections) (February 1, 2009) (section titled *Labels and Labeling; Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products*); see also FDA Guidance for Industry, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" (May 2022) at 14-15 ("For small-volume injection products, the product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling").

[51] See *id.*; see also FDA Guidance for Industry, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" (May 2022) at 14 ("If the product strength is not clearly displayed on the container label or carton labeling, or if it is expressed in units of measure that are incongruent with those used in the DOSAGE AND ADMINISTRATION section of the [package insert], the wrong strength can be selected or the wrong dose administered (i.e., over- or under-dosing).").

reflected in FDA's modification to the display of strength in the Orange Book (discussed in section II.A of this response), and was "reinforced" by certain FDA regulations and documents that referred to "strength or concentration" but were not specific to parenteral solutions (see Petition at 13-14). For example, BI contends that "strength" and "concentration" are treated as separate regulatory concepts in FDA's bioequivalence regulations based on criteria for waiver of in vivo BE testing for different strengths and for parenteral drug products with the same active and inactive ingredients in the same concentration as the RLD (see Petition at 13-14; see also see also § 320.22(b)(1)(ii) and (d)(2) (21 CFR 320.22(b)(1)(ii) and (d)(2))). BI also refers to FDA regulations requiring sponsors to obtain a new National Drug Code (NDC) number if there is any change in "strength or concentration" (21 CFR 207.35). In addition, BI refers to the preamble to the 2009 Orange Book, which defined "pharmaceutical equivalents" to mean drug products that are, inter alia, "identical in strength or concentration."[52] BI also observes that FDA's 2004 "bundling guidance" informs sponsors that FDA will accept several "different strengths or concentrations" of a drug product within a single NDA.[53]

BI contends that "[w]hen Congress referenced 'strength' – but not 'concentration' – in the [BPCI Act], 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" (Petition at 13). BI asserts that "[a]lthough FDA's implementing regulations impose a "same concentration" requirement for parenteral drugs, this requirement applies solely to *inactive ingredients*… 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*." (Petition at 14) (emphasis in original; internal citations omitted).

FDA Response:

We disagree with BI's statement that "'strength' and 'concentration' had distinct, non-overlapping meanings when the [BPCI Act] was enacted" (Petition at 12). We also disagree with BI's assertion that FDA's interpretation of the "strength" of a parenteral solution for purposes of section 505(j)(2)(A)(iii) of the FD&C Act did not include the concentration of drug substance before 2016.[54]

Although BI asserts that the definition of "strength" in § 210.3(b)(16) "is a highly specialized definition that applies solely to cGMP issues… [and c]onsequently, it is not relevant for purposes of defining 'strength' in the context of the Hatch-Waxman Act or the BPCIA," (Petition at 10, note 20) we begin with this definition, which informed the Agency's approach. The following definition of "strength" in § 210.3(b)(16) predates enactment of the Hatch-Waxman

[52] Petition at 13 (citing Orange Book, 29th ed. (2009) at vii).

[53] Petition at 13-14 (citing FDA Guidance for Industry, "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" (December 2004) at 4).

[54] See generally section II.A of this response, see also FDA Draft Guidance for Industry "ANDA Submissions – Refuse-to-Receive Standards" (October 2013) (FDA-2013-D-1120-0002) at 16 ("ANDA parenteral (injectable) drug products should contain the same concentration and total drug content per container as the RLD"). This principle is unchanged in the final guidance (FDA Guidance for Industry "ANDA Submissions – Refuse-to-Receive Standards" (Rev. 2, December 2016) at 12-13).

Amendments and reflects the Agency's longstanding position that concentration is an integral part of "strength" for certain types of drug and biological products:

> *Strength* means: (i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or (ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).[55]

The definition of "strength" in § 210.3(b)(16) plainly evidences that "concentration" is one element of "strength," depending on the dosage form.

FDA's bioequivalence (BE) regulations in § 320.22 do not support BI's assertion that "strength" and "concentration" are treated as separate regulatory concepts. Concentration is broken out as a component of strength for some dosage forms and in certain contexts but not in others and this difference is reflected in FDA's BE regulations. Section 320.22 sets forth the criteria for an applicant to request that FDA waive the requirements for the submission of evidence measuring the in vivo bioavailability (BA) or demonstrating the in vivo BE of the drug product as compared to another drug product.[56] For certain drug products for which in vivo BA or BE may be self-evident (e.g., certain parenteral solutions), FDA will grant a "biowaiver" under § 320.22(b) if specified criteria are met. For example, if the drug product is a parenteral solution intended solely for administration by injection and "[c]ontains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full [NDA or ANDA]," FDA will grant a biowaiver because in vivo BA or BE may be considered self-evident based on other data in the application.[57,58]

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[55] "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding"; final rule, 43 FR 45014, 45077 (September 29, 1978).

[56] See § 320.22; see also "Abbreviated New Drug Application Regulations"; final rule, 57 FR 17950, 17998 (April 28, 1992), as amended by "Bioavailability and Bioequivalence Requirements; Abbreviated Applications"; final rule, 67 FR 77668, 77673 (December 19, 2002). The 2002 amendments did not substantively change the meaning of § 320.22(b) or (d) as relevant here.

[57] See 21 CFR 320.22(b)(1)(i).

[58] The regulation at § 314.94(a)(9)(iii) (21 CFR 314.94(a)(9)(iii)) requires that—aside from the "exception excipients" of preservative, buffer, or antioxidant—generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the RLD. We note that § 314.94(a)(9)(iii), which relates to inactive ingredient sameness, does not compel that a generic drug product that is a parenteral solution must have the same concentration of *active* ingredient as the RLD. It may be possible to modify the concentration of the active ingredient, which may necessitate certain changes to the concentration of an inactive ingredient(s), and simultaneously meet the requirements of § 314.94(a)(9)(iii) and fail the requirements of 21 CFR 314.94(a)(6) with respect to same "strength." In other words, certain differences in the concentration of an inactive ingredient between a proposed generic drug product that is a parenteral solution and its RLD may or may not be permissible under § 314.94(a)(9)(iii), depending on the extent of the difference and which inactive ingredient's concentration differs, and do not compel a difference in the concentration of the active ingredient.

Section 320.22(d)(2) of the regulations, on the other hand, describes circumstances in which certain drug products in the same dosage form, but in a different strength, from another product approved from the same manufacturer can use in vitro evidence and evidence of proportional similarity of active and inactive ingredients to its approved drug product rather than in vivo data to measure BA or to demonstrate BE. The use of the term "strength" in this context reflects that this regulation applies to drug products in the same dosage form and same product line (typically different strengths of the same solid oral dosage form from the same sponsor); accordingly, evaluation of whether the criterion of "different strength" is met would be based on the weights and measures appropriate to the type of drug product and dosage form. For example, "the strength of a solid oral dosage form is determined only by the total quantity of drug substance in a dosage unit (e.g., a 25-milligram (mg) tablet)."[59] The term "strength" is used in § 320.22(d) because the concept of concentration (mass per volume) used for a liquid does not apply to a solid, and therefore concentration is not relevant to the strength of each of the dosage forms encompassed within this subsection of the regulation. Thus, FDA's use of the terms "strength" and "concentration" in different places in its BE regulations reflects the Agency's view that "concentration" is an element of strength for certain products (e.g., parenteral solutions) but is not typically broken out for others (e.g., solid oral dosage forms) and that the terms have overlapping meanings.

Moreover, the use of the phrase "identical in strength or concentration" in an earlier description of "pharmaceutical equivalents"[60] in the Orange Book does not support BI's contention, given that other text makes clear that concentration is an element of strength and thus there is overlap between the terms "strength" and "concentration." For example, the Orange Book explains: "The codes in this book are not intended to preclude health care professionals from converting pharmaceutically different concentrations into pharmaceutical equivalents using accepted professional practice."[61] Thus, differences in concentration between a generic drug product that is a parenteral solution and its RLD mean that the products are not pharmaceutical equivalents (and therefore also are not therapeutic equivalents) because they do not have the same strength.

BI's references to "strength or concentration" in the context of changes that would require a new NDC number or changes that may be submitted within a single NDA are similarly unavailing, and do not support BI's contention that strength is distinct from concentration.

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[59] "Abbreviated New Drug Applications and 505(b)(2) Applications"; proposed rule, 80 FR 6802, 6816, February 6, 2015).

[60] See Orange Book, 29th ed. (2009) at vi ("Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide [HCl], 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity) but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling."); compare 21 CFR 320.1(c) (2009) ("pharmaceutical equivalents means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient…").

[61] Orange Book, 29th ed. (2009) at xv.

C. FDA's Interpretation of the "Strength" of "Injection" and "For Injection" Products is Scientifically Justified

BI asserts that "[a]lthough 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" (Petition at 22). BI refers to FDA's longstanding practice of evaluating the "strength" of a drug product in a "for injection" dosage form (e.g., a lyophilized powder) based on the total drug content in the container without regard to the concentration after reconstitution (see Petition at 21). BI contends that FDA's interpretation of "strength" is arbitrary and capricious in violation of the Administrative Procedure Act (5 U.S.C. 706(2)(A) because there is "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" (Petition at 22).

FDA Response:

FDA's interpretation of the term "strength" appropriately reflects that the weights and measures used to determine the strength of a drug product may differ based on the type of drug product or dosage form.[62] As BI notes, FDA considers "injection" (e.g., a solution) to be a different dosage form than "for injection" (e.g., a lyophilized powder).[63] A product in an "injection" dosage form (e.g., a solution) inherently involves two components: a solute that includes the drug substance and a solvent acting as a vehicle in which the solute is dissolved. A product in a "for injection" dosage form (e.g., a lyophilized powder) is generally a "solid" and not a "liquid." Thus, it is scientifically appropriate for the strength of a "for injection" dosage form to be determined based on the total content of drug substance in the container closure because the concept of concentration (mass per volume) used for a liquid does not apply to a solid. Accordingly, we disagree with BI's contention that "injection" and "for injection" dosage forms are similarly situated for purposes of strength determinations under the BPCI Act.[64]

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[62] See section I.B of this response.

[63] See, e.g., Eloxatin Petition Response; see also FDA Guidance for Industry, "Questions and Answers on Biosimilar Development and the BPCI Act" (Rev. 2, September 2021) at Q&A I.18 and section I.C of this response.

[64] See also section 351(k)(2)(A)(i)(IV) of the PHS Act (requiring, among other things, that a 351(k) applicant must demonstrate that the "dosage form" of the proposed biosimilar or interchangeable biosimilar product is the same as that of the reference product). Accordingly, 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" because these are different dosage forms. . See FDA Guidance for Industry, "Questions and Answers on Biosimilar Development and the BPCI Act" (Rev. 2, September 2021) at Q&A I.18. Similarly, drug products regulated under the FD&C Act in an injection dosage form are considered pharmaceutical alternatives, not pharmaceutical equivalents, to drug products in a for injection dosage form. In 2008, the Orange Book was revised to state: "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" (Orange Book, 28th ed. (2008), at xvi).

In general, for a proposed biosimilar or interchangeable biosimilar product in a "for injection" dosage form (e.g., a dry solid such as 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).[65] FDA has explained that, although not a part of demonstrating same "strength," if the proposed biosimilar or interchangeable biosimilar product is a dry solid (e.g., a lyophilized powder) from which a constituted or reconstituted solution is prepared, the 351(k) BLA "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."[66] This reflects, among other things, that the Dosage and Administration section of product labeling is required to include information on the concentration(s) of the product when constituted or reconstituted, and the Agency evaluates the safety, purity, and potency of the reference product at the concentration(s) listed in the labeling.[67] This interpretation aligns with the approach used to establish the strength of proposed generic drug product in a "for injection" dosage form.

Although drug and biological products in an "injection" dosage form (e.g., a solution) and a "for injection" dosage form (e.g., a lyophilized powder) are necessarily administered to patients as a solution, differences associated with the properties of the two dosage forms and preparation of the product prior to administration can raise distinct risks of confusion and patient safety. For example, drug products supplied as solutions with the dosage form "injection" may require further dilution and/or dose adjustment based on a patient's body weight, route of administration, or the designated maximum concentration obtainable. To ensure accurate dose through proper dilution, it is critical to know the concentration of the drug substance in addition to the total drug content.[68]

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[65] See FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)" (September 2021) at Q&A I.12.

[66] See FDA Draft Guidance for Industry, "New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 3)" (September 2021) at Q&A I.12.

[67] See 21 CFR 201.57(c)(3) ("Dosage and administration (i) This section must state the recommended dose and, as appropriate: (iv) This section must also contain specific direction on dilution, preparation (including the strength of the final dosage solution, when prepared according to instructions, in terms of milligrams of active ingredient per milliliter of reconstituted solution, unless another measure of the strength is more appropriate), and administration of the dosage form, if needed (e.g., the rate of administration of parenteral drug in milligrams per minute; storage conditions for stability of the reconstituted drug, when important; essential information on drug incompatibilities if the drug is mixed in vitro with other drugs or diluents; …").

[68] See, e.g., Drugs@FDA, Heparin sodium injection (NDA 017037), Label (Dec. 23, 2011), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017037s169.pdf, at 3 ("Fatal Medication Errors. … Heparin Sodium Injection is supplied in vials containing various strengths of heparin, including vials that contain a highly concentrated solution of 10,000 units in 1 mL. Fatal hemorrhages have occurred in pediatric patients due to medication errors in which 1 mL Heparin Sodium Injection vials were confused with 1 mL 'catheter lock flush' vials. Carefully examine all Heparin Sodium Injection vials to confirm the correct vial choice prior to administration of the drug."). Due to the potential for medication errors in heparin sodium injection and heparin lock flush solution, the labels for each drug product were updated to more clearly describe the strength of each product.

D. FDA's Interpretation of "Strength" is Scientifically Justified

BI asserts that FDA's interpretation of the term "strength" in section 351(k) of the PHS Act is unreasonable because it "subverts the goals of the BPCIA in at least two ways" (Petition at 16). First, BI contends that "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" (Petition at 16). Specifically, BI states that "[b]y changing the concentration of the RP [reference product] 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," which BI characterizes as a "product hopping" tactic (see Petition at 18). BI contends that "[i]f 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" (Petition at 18).

Second, BI asserts that FDA's interpretation of strength "undermines the BPCIA's goal of speeding the development and availability of biosimilar and interchangeable biological products, with no legitimate countervailing regulatory purpose" (Petition at 19; see also Petition at 16). Specifically, BI states "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')" (Petition at 19). BI opines that "[i]n many cases, injectable products having the same total drug content but different concentrations exhibit no differences in safety, effectiveness, operation, or directions for use. 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" (Petition at 19).

Finally, BI proposes that "[i]f 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 the concentration difference is so significant as to preclude a finding of 'highly similar' to the [reference product] notwithstanding minor differences in clinically inactive components or results in 'clinically meaningful differences' between the products…. 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 [reference product] in any given patient because of, for instance, different or more frequent adverse events…" (Petition at 20 (internal citations omitted)).

A comment submitted by Dr. Niazi proposes that "[t]he correct argument for seeking a reinterpretation of 'concentration' should be based on the BPCIA description that a biosimilar product may have different inactive ingredients. When a formulation is changed for whatever reason, the optimization of the solution's thermodynamic stability may require a different

concentration. So, if a different formulation is allowed, it should also be allowed to have a different concentration, higher or lower" (Niazi Comment at 2).[69]

FDA Response:

FDA's approach to the interpretation of "strength" in the context of a proposed biosimilar or interchangeable biosimilar product with an "injection" dosage form (e.g., a liquid parenteral product) aligns with the Agency's longstanding interpretation of the term "strength" in the context of generic drug requirements in a nearly identical phrase in section 505(j) of the FD&C Act,[70] and also reflects scientific consideration of the potential for differences in the concentration of liquid parenteral products that could result in medication errors, potential differences in certain quality attributes, and potential differences in the PK and, where applicable, pharmacodynamic (PD) profile.

For example, as explained in section II.D of this response, differences in concentration can result in medication errors, including incorrect dosing of patients (overdosing or underdosing), which can impact safety and efficacy. This is a particular concern where the dose is calculated based on the patient's weight or if the healthcare practitioner or patient needs to administer less than all of the contents of a container (e.g., a vial or prefilled syringe) or needs multiple containers to administer a complete dose.[71] Products that are available as single-dose vials are generally prepared or administered by withdrawing the full or partial content of the vials. In those instances, not having the total amount per total volume and concentration clearly identified on the vial (or being unaware of a difference in concentration) may lead to inaccurate calculation of the volume needed to prepare or administer a dose, which may lead to underdosing or overdosing. Thus, it is important for the end user to be aware of the total drug content as well as concentration in the vial to avoid dosing errors.

Additionally, any changes in concentration may lead to dosing errors as well. If the biosimilar or interchangeable product were marketed with a different concentration as compared to the reference product, this may predispose users, who have acquired certain knowledge and behavior over time with the reference product, to overlook the change in concentration. Additionally, if the total drug content remained the same, but concentration changes, it is foreseeable that healthcare practitioners would withdraw the same volume that they are accustomed to withdrawing with the reference product, without regard to the change in concentration, resulting in dosing errors.

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[69] Comment dated December 12, 2020, from Sarfaraz K. Niazi, Ph.D. (FDA-2020-P-2247-0015) (Niazi Comment); see also comment dated December 14, 2020, from Sarfaraz K. Niazi, Ph.D. (FDA-2020-P-2247-0016).

[70] See, e.g., Sekhar v. U.S., 570 U.S. 729, 733 (2013) (citing Justice Frankfurter's 1947 statement that "'if a word is obviously transplanted from another legal source, whether the common law or other legislation, it brings the old soil with it.'"); see also sections I.A to I.C and II.A of this response.

[71] As discussed later in this section, a single-dose autoinjector generally cannot be manipulated to deliver less than the stated contents. As such, for products in an autoinjector presentation, differences in concentration may not present safety risks associated with medication error or administration (if supported by adequate data), although other potential risks (e.g., product quality, PK/PD, and immunogenicity) may still apply.

Even if the risk of dosing and administration errors can be mitigated, differences in drug substance concentration also can affect certain product quality attributes (e.g., viscosity or aggregation), which can impact a product's safety and effectiveness.[72] For example, certain biological products may be more susceptible to aggregation at higher drug substance concentrations, which can affect the PK profile or risk of immunogenicity. Biological products with different drug substance concentrations also may exhibit differences in stability profiles due to different degradation products (such as aggregation and oxidation), which may, for example, lead to higher immunogenicity risk for certain biological products or reduced biological activity that potentially impacts efficacy. In this regard, we disagree with Dr. Niazi's assertion that a proposed biosimilar or interchangeable biosimilar should be permitted to have a different concentration from the reference product solely because formulation differences are allowed. The optimization of formulation to support stability may be achieved through several means without the need to change the concentration of product, including changes in formulation design such as a change in inactive ingredients and design of the manufacturing process.[73]

Differences in drug concentration, especially for biological products such as monoclonal antibodies administered subcutaneously, along with potential differences in formulation, also could lead to differences in the PK or PD profile, even if the biological product contains the same total quantity of drug substance.[74] In general, the subcutaneous administration of therapeutic proteins, especially monoclonal antibodies, involves an absorption process from the site of injection that is governed primarily by: (1) passive diffusion and convective mechanisms through the interstitial space into the lymphatic network[75]; and (2) lymphatic transport eventually draining into the systemic circulation. Both processes are relatively slow leading to slow increase in plasma concentration; however, the rate-limiting step is interstitial transport.[76] As

[72] See, e.g., Zarzar J, Khan T, Bhagawati M, et al. "High concentration formulation developability approaches and considerations." mAbs. 2023;15:1-13 (observing that "high concentration mAb [monoclonal antibody] formulations can pose substantial manufacturing, stability, and delivery challenges. As protein concentrations have increased, so has the occurrence of physical instability (e.g., opalescence, aggregation, particles) and viscosity challenges").

[73] See, e.g., Maroju RK, Barash S, and Brisbane CE. "Evaluation of a Biologic Formulation Using Customized Design of Experiment and Novel Multidimensional Robustness Diagrams." J Pharm Sci 2018;107(3):797-806 (noting that "[f]ormulation development includes selection of appropriate excipients to stabilize the active pharmaceutical ingredient throughout its recommended shelf life, against potential excursions in its life cycle and sometimes to aid in the delivery of therapeutics into the patient").

[74] This is the case for High Concentration Humira, which differs in formulation and concentration from Original Concentration Humira. High Concentration Humira "provides a slightly higher exposure compared to the [original concentration (50 mg/mL) of Humira] … across all PK parameters. Notwithstanding this higher exposure, the sponsor provided adequate justification and data in its application to support licensure of High Concentration Humira and FDA determined that the overall safety and effectiveness profile of the 100 mg/mL formulation (high concentration) was consistent with the safety and effectiveness profile of the approved 50 mg/mL formulation (low concentration). This conclusion was based on, among other things, historical adalimumab data in the Humira BLA (including the original clinical program to support licensure in the RA population) and descriptive results from a small clinical study (see FDA Division Summary Review for BLA 125057, Supplement 394, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125057Orig1s394SumR.pdf).

[75] See, e.g., Richter WF, Bhansali SG, Morris ME. "Mechanistic determinants of biotherapeutics absorption following SC administration." AAPS J. 2012;14(3):559-70.

[76] See, e.g., Richter WF, Bhansali SG, Morris ME. "Mechanistic determinants of biotherapeutics absorption following SC administration." AAPS J. 2012;14(3):559-70.

such, a change in drug substance concentration that affects the product quality profile (e.g., viscosity or aggregation) also could affect not only the rate but also the extent of the absorption of the biological product, leading to a different PK profile.

Accordingly, we disagree that, as a general matter, differences in drug substance concentration are often not clinically meaningful.[77] We note, however, that there may be certain scenarios in which biological products in an injection dosage form (e.g., a parenteral solution) having the same total drug content but different concentrations do not exhibit differences in safety, effectiveness, operation, or directions for use. For example, this may depend, among other things, on whether the product is a single-dose or multi-dose product and the type of delivery device used to administer the product. For biological products in a single-dose presentation (e.g., a biological product delivered via autoinjector or prefilled syringe), where the entire content is administered and the product is not labeled for doses requiring administration of less than the entire content, different concentrations of the same total drug content may not affect safety, effectiveness or directions for use, provided that the applicant provides adequate data to demonstrate that there is no impact on quality attributes or the PK profile and the difference in concentration otherwise does not alter the safety and effectiveness profile of the product. This scenario assumes that the delivery devices for both biological products do not have differences in user interface design that impact critical tasks.[78] In addition, for certain multiple dose products that utilize single-patient use pen injectors that dial a dose based on the specific amount of drug (without regard to volume), differences in concentrations between products are unlikely to lead to a change in directions for use or raise medication error or usability concerns, provided that both products do not have any differences in device user interface design that impact critical tasks. Although such scenarios may not raise the same level of concern for medication or dosing errors, the Agency has chosen to adopt an interpretation of the statutory term "strength" (which consists of a single term that does not explicitly distinguish such factual differences) that would remain consistent across the range of products to which the term applies.

Moreover, it is also possible while the originally approved dosing regimen for a reference product (and any biosimilar and interchangeable biosimilar products to that reference product) may require that the entire contents of a syringe be administered, there may be instances where addition of subsequent indications or patient populations may require dosing of less than the entire content from a prefilled syringe. In these cases, a difference in concentration could raise

[77] Although BI refers to "minor differences" in drug substance concentration, it is unclear what difference in concentration would be considered "minor" and for which product(s). With respect to BI's assertion that "[t]o 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" (Petition at 17), we note that a one-drop difference in water content would not necessarily preclude a finding of biosimilarity or interchangeability for a biological product (or a determination of therapeutic equivalence for a drug product). In this regard, we note that due to variability in the manufacturing processes and test methods, release specifications for many biological products allow variability around nominal values. In such instances, we disagree with BI's broad assertion that minor concentration changes by the BLA holder for a reference product would be used as an anti-competitive tactic to prevent competition from biosimilar and interchangeable biological products.

[78] Critical tasks for combination products are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care. See FDA Guidance for Industry and FDA Staff, "Application of Human Factors Engineering Principles for Combination Products: Questions and Answers" (September 2023).

questions of safety (including a risk of dosing errors when calculating the correct volume necessary to prepare or administer a dose) or effectiveness, as well as other questions regarding licensure, even where the originally approved concentrations did not.

The BPCI Act does not allow FDA to determine that a demonstration of same strength is unnecessary in a 351(k) BLA, provided that sufficient information is submitted to support a demonstration of biosimilarity, or to allow a proposed biosimilar product to deviate from the reference product in strength.[79] We acknowledge that a BLA holder for the reference product could seek approval for a new strength of its biological product in an injection dosage form—either by changing the total content of drug substance or the concentration—and discontinue marketing a previously approved strength as part of a broader effort to inhibit competition. As a general matter, an applicant could receive licensure for a discontinued strength of the reference product. In addition, a 351(k) applicant seeking licensure of a biosimilar or interchangeable biosimilar product in a strength for which there is a newly approved reference product may be able to leverage certain existing data developed with another strength, if scientifically justified, to support licensure of the proposed biosimilar or interchangeable biosimilar product. Accordingly, although, as the petitioner notes, there might be hurdles to seeking licensure in these situations, we do not believe that there are outright barriers to the development of a proposed biosimilar or interchangeable product where the reference product obtains approval for a new strength and discontinues marketing a previously approved strength. Currently, there are several approved biosimilar adalimumab products to Humira, including approved biosimilars that have the same total drug content and same concentration as High Concentration Humira (see table in section I.D of this response).

E. Potential Implications of BI's Proposed Change to FDA's Interpretation of Strength

BI asserts that "even assuming [BI'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" (Petition at 2; see also Petition at 22). BI also maintains that "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." (Petition at 22-23).

[79] We also note that the conditions of use of the biosimilar or interchangeable biosimilar product must have been previously approved for the reference product, so the addition of new dosing regimens that have not been previously approved for the reference product (e.g., which could be needed due to a difference in concentration) would not be permissible under section 351(k)(2)(A)(i)(III) of the PHS Act. In this regard, we disagree with the Pharmaceutical Care Management Association's assertion that "[b]iosimilars approved under a recast definition of strength could differ from the reference product with regards to composition and dosing, while retaining the same levels of safety and efficacy… With proper labeling and well-executed prescriber education regarding any dosing differences, licensed biosimilars whose concentrations differ from the reference product should successfully bring needed competition to the market" (comment dated March 19, 2021, from Pharmaceutical Care Management Association (Docket No. FDA-2020-P-2247-0017) at 2-3 (PCMA Comment).

FDA Response:

For the reasons discussed earlier in this response, we disagree that FDA should adopt BI's proposed interpretation of "strength" for biological products in an injection dosage form (e.g., parenteral solutions) to include only total content of drug substance and not to include concentration.

In the context of biological products regulated under the PHS Act, such an approach would raise a number of countervailing regulatory interests. For example, under BI's interpretation, injection products with different concentrations but the same total content of drug substance would be considered the same reference product, which could result in a proliferation of biosimilar[80] or interchangeable biosimilar products with different concentrations from the reference product, which could raise concerns regarding medication errors.[81]

BI's approach also could create concerns with respect to biosimilar or interchangeable biosimilar products that differ in concentration from the reference product if there are certain changes to the reference product over the product lifecycle. Such concerns could arise, for example, if the reference product were approved for a new indication with weight-based dosing or in a new single- or multiple-dose presentation in which the entire content is not expected to be administered.

We also note that BI's proposed interpretation of "strength" may result in broader exclusivity that blocks a wider range of products from being licensed as interchangeable under section 351(k)(6) of the PHS Act for eligible first interchangeable products. Because eligibility for such exclusivity is associated with the first interchangeable product to a particular reference product, and we generally consider different "strengths" of a product to be different reference products, if multiple concentrations with the same total drug content were considered the same strength and therefore the same reference product, first interchangeable exclusivity for one concentration would block FDA from approving as interchangeable another product with a different concentration but the same total drug content. For example, if a 351(k) BLA holder has unexpired first interchangeable exclusivity for a particular "strength" of its interchangeable biosimilar product in an injection dosage form, under BI's interpretation of "strength," the 351(k) BLA holder would be able to block licensure of competing biosimilar products that contain the same total drug content in any concentration as interchangeable with the reference product.

Finally, in the absence of a scientific rationale for why parenteral solutions regulated as biological products under the PHS Act inherently differ from parenteral solutions regulated as

[80] See, e.g., PCMA Comment at 2 ("A change in FDA's interpretation of strength to allow for varying concentration should increase the number of biosimilar products on the market").

[81] We note, however, that in scenarios in which the entire contents are to be administered from a biological product in a single-dose presentation such as an autoinjector or prefilled syringe or for certain single-patient-use products where the user selects a dose of an injectable product by dialing the intended dose without a need to calculate or measure the dose, it is unlikely that changes in directions for use for the proposed product would be needed or that users would encounter new usability issues.

drug products under the FD&C Act, BI's proposed interpretation of strength, if adopted, would have potentially disruptive implications for drug products regulated under the FD&C Act.

As noted in section I of this response, it is FDA's longstanding practice to regard different strengths of a drug product as different drug products, and thus each strength of a drug product approved in an NDA can be designated as the RLD for a generic drug product. FDA's longstanding interpretation of strength in the context of parenteral solutions regulated under the FD&C Act informs, for example, FDA's approach to: RLD designations; suitability petitions submitted under section 505(j)(2)(C) of the FD&C Act; filing and approval of ANDAs under section 505(j) of the FD&C Act; 180-day exclusivity determinations under section 505(j)(5)(B)(iv) and (v) of the FD&C Act[82]; therapeutic equivalence evaluations[83]; and the "different strength" exception to the limitation on submission of certain amendments and supplements to a 505(b)(2) application or an ANDA in section 505(b)(4)(B) and (j)(2)(D)(ii) of the FD&C Act. Accordingly, a change in the Agency's interpretation to mean "total drug content" only in the relevant container without regard to concentration could disrupt well-established practices for parenteral solutions regulated under the FD&C Act.

III. CONCLUSION

Based on the reasons described in this response, we deny your request.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2024.02.23 11:52:44 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[82] Different strengths are considered different drug products and are therefore eligible for separate periods of 180-day exclusivity.

[83] Under BI's proposed interpretation, two products with the same total amount of drug substance but with different concentrations (e.g., Precedex (dexmedetomidine HCl) injection, 200 mcg/2 mL and Precedex (dexmedetomidine HCl) in 0.9% sodium chloride injection, 200 mcg/50 mL) would meet the "same strength" criterion for the pharmaceutical equivalence component of a therapeutic equivalence evaluation because they have the same total drug content.