Boehringer Ingelheim

VIA ELECTRONIC SUBMISSION

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Re: Citizen Petition Requesting the Food and Drug Administration to Make Strength Determinations for Parenteral Biologics Based Upon the Total Drug Content of the Container Without Regard to Concentration

Dear Sir or Madam:

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

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

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

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

I. Actions Requested

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

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

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

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

The grounds for these requests are set forth in detail below.

II. Statement of Grounds

A. FDA's Final Interpretation of "Strength" and Its Harm to the Regulated Industry

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

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

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

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

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

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

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

Finally, and particularly relevant here, FDA cannot approve a biological product under the 351(k) pathway unless – like a proposed generic drug seeking approval under the Hatch-Waxman

Act's Abbreviated New Drug Application ("ANDA") pathway – it has the same "strength" as the RP. *Id*. § 262(k)(2)(A)(i)(IV).

2. FDA's Final Interpretation of "Strength" in the BPCIA

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

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

FDA, *Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, p. 10 (Feb. 2012) ("2012 Draft Guidance") (Exhibit 1).

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

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

> In general, a sponsor of a proposed biosimilar product or proposed interchangeable product with an "injection" dosage form (e.g., a solution) can demonstrate that its product has the same strength as the reference product by demonstrating that both products have the same total content of drug substance (in mass or units of activity) *and the same concentration of drug substance* (in mass or units of activity per unit volume).

2018 Draft Q&A Guidance, p. 5 (emphasis added).

This Agency position has been expressed consistently throughout the various iterations of the guidance documents (both draft and final) since at least 2012. Although the current guidance is styled as a "draft," there is no indication that FDA's interpretation of "strength" as applied to "injection" dosage forms (*i.e.*, parenteral solutions) is under active consideration. On the contrary, it appears FDA moved the discussion of "strength" from final to draft form in 2018 solely because of proposed changes to how strength is determined *for dry solids from which a constituted or reconstituted solution is prepared* (*e.g.*, lyophilized powders), not because FDA is reconsidering how strength is determined for parenteral solutions.

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

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

3. Adalimumab Biological Products

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

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

products have been licensed by FDA via the 351(k) pathway, each of which is approved only as a 50 mg/mL concentration formulation.

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

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

FDA's final interpretation of "strength" has a direct and immediate impact on members of the regulated industry.[1] FDA's interpretation prevents a biological product with the same total drug content but a different concentration than the RP from being licensed as a biosimilar or interchangeable biological product, thereby impairing price competition and access to affordable biological products. Biosimilar manufacturers and/or sponsors, including Boehringer Ingelheim, are currently left with no option but to invest in the expensive and time-consuming process of developing biosimilar products with identical concentrations to the relevant RP *even if* they can prove that the proposed product is highly similar to and produces the same clinical results in terms of safety, purity, and potency as all concentrations of the RP. That hurts manufacturers, sponsors, and patients, and is contrary to the intent of the BPCIA.

B. FDA's Interpretation of "Strength" Conflicts With the BPCIA, Is Unreasonable, and Is Arbitrary and Capricious

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

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

1. Legal Standard

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

Because FDA's interpretation of the BPCIA may be subject to judicial review, FDA's interpretation of the BPCIA definition of "strength" must be analyzed under the well-known, two-step *Chevron* test established by the U.S. Supreme Court in 1984.[2] Under the first step, a reviewing court must determine "whether Congress has directly spoken to the precise question at issue."[3] If the statutory language is plain and unambiguous and "the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress."[4]

In making this determination, courts apply traditional tools of statutory construction to determine Congressional intent, including an examination of the statute's text, structure, and purpose, as well as use of established canons of statutory construction.[5] Typically, the statutory language itself and the structure and purpose of the statute as a whole are the most powerful indicators of Congressional intent.[6] In addition, courts are careful not to interpret a statutory provision in isolation but instead strive to consider the context in which it is used, taking into account the entire statutory scheme and the overriding goals of the legislation.[7]

If a court concludes that the statute is either silent or ambiguous on the precise question at issue, the second *Chevron* step is to determine whether the interpretation proffered by the agency is "based on a permissible construction of the statute."[8] "[A]mbiguity is not a license for the FDA

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[2] *Chevron U.S.A. Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984), *reh'g denied* 468 U.S. 1227 (1984); *see also Kisor v. Wilkie*, 139 S.Ct. 2400 (2019).

[3] *Eagle Pharms., Inc. v. Azar*, 952 F.3d 323 (D.C. Cir. 2020) (quoting *Chevron*, 467 U.S. at 842); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1067 (D.C. Cir. 1998) (same).

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

[5] *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998); *Bell Atl. Tel. Co. v. FCC*, 131 F.3d 1044, 1047 (D.C. Cir. 1997); *Amarin Pharms. Ir. Ltd. v. FDA*, 106 F. Supp. 3d 196, 207 (D.D.C. 2015); *Stat-Trade Inc. v. FDA*, 869 F. Supp. 2d 95, 102 (D.D.C. 2012).

[6] *See Amalgamated Transit Union v. Skinner*, 894 F.2d 1362, 1368 (D.C. Cir. 1990) (quoting *K Mart Corp. v. Cartier, Inc.,* 486 U.S. 281, 291 (1988)); *Watson Labs, Inc. v. Sebelius*, 2012 U.S. Dist. LEXIS 185685, at *25-*26 (D.D.C. Oct. 22, 2012), *vacated as moot*, 2013 U.S. App. LEXIS 11716 (D.C. Cir. 2013) (internal citation and quotation omitted).

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

[8] *Chevron*, 467 U.S. at 843.

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

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

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

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[9] *Braeburn, Inc. v. FDA*, 389 F. Supp. 3d 1, 23 (D.D.C. 2019).

[10] *Id*.

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

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

[13] *Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 52 (1983).

[14] *Id*. at 43.

[15] *Ferring Pharms., Inc. v. Burwell*, 2016 U.S. Dist LEXIS 121826, at *25 (D.D.C. Sept. 9, 2016) (quoting *Indep. Petroleum Ass'n of Am. v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996)).

[16] *Etelson v. Office of Pers. Mgmt.*, 684 F.2d 918, 926 (D.C. Cir. 1982).

[17] *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (quoting *Allergan, Inc. v. Shalala*, 6 Food and Drug Rep. 389, 391, No. 94-1223 (D.D.C. Nov. 10, 1994) (Greene, J.)).

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

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

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

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

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

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[18] *Sandoz, Inc. v. Amgen*, 773 F.3d 1274 (Fed. Cir. 2014) (noting that Congress borrowed from Hatch-Waxman's ANDA process when enacting the BPCIA); *Pfizer, Inc. v. Johnson & Johnson*, 333 F. Supp. 3d 494, 497 (E.D. Pa. 2018) (BPCIA created abbreviated approval system similar to the process for generic drugs under Hatch-Waxman); *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 2018 U.S. Dist. LEXIS 233075, at *9 (D.Mass. Sept. 27, 2018) (BPCIA borrowed from Hatch-Waxman's ANDA process).

[19] *See Amgen v. Sandoz*, 877 F.3d 1315, 1320 (Fed. Cir. 2017) (noting that BPCIA "has certain similarities in its goals and procedures to the [Hatch-Waxman Act]," although it also has several obvious differences).

term was not explicitly defined in either the statute or FDA's implementing regulations,[20] FDA defined the term precisely in its publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book. The Orange Book is a highly relevant source for ascertaining FDA's definition of "strength" for purposes of the Hatch-Waxman Act because it is the only Agency publication specifically referenced in the Hatch-Waxman Act. *See* 21 U.S.C. § 355(j)(7)(A). Notably, FDA regulations require the Orange Book to contain information about, among other things, the "strength" of all listed drug products. *See* 21 C.F.R. § 20.117(a)(3) (requiring public availability of a list of approved drugs, including the "strength").

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

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

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

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

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

[21] *MCI Telecomms. Corp. v. AT&T Co*., 512 U.S. 218, 228 (1994) (identifying the time of enactment as "the most relevant time for determining a statutory term's meaning"); *Rouse v. Wachovia Mort., FSB*, 747 F.3d 707, 714 (9th Cir. 2014) ("In interpreting Congressional intent, we look to the time of Congress's enactment of the legislation."). Moreover, although there are some FDA statements indicating that a change in concentration may be considered a change in strength (*e.g.*, FDA Response to Sterling Winthrop Petition, Docket No. 92P-0224 (Sept. 11, 1992); FDA Response to OFW Petition, FDA-2004-P-0418 (June 19, 2012)), these all appear to have been made either prior to FDA's 2003 changes to the Orange Book or after passage of the BPCIA. Accordingly, they are not relevant for purposes of determining Congressional intent *at the time the BPCIA was enacted*. In any event, they do not override the clear and unequivocal statements made in the Orange Book, which would have been the most conspicuous and authoritative evidence of the definition of "strength" available to Congress at that time.

Accordingly, around 2003, FDA began displaying the strength of parenteral drug products – the total drug content per container – in addition to the concentration (*e.g.*, 1Gm/20mL (50mg/ml)). FDA continued to display the concentration of parenteral solutions in accordance with its past practice, while making clear that concentration was not a component of the "strength" of such drugs; rather, under the Hatch-Waxman Act, the strength of a parenteral drug was limited to the total drug content of the relevant container. *See* Orange Book, p. xvii (2009) ("Until recently the strength of liquid parenteral drugs products in the Orange Book have not been displayed[,]" only the concentration.). Consequently, the 2003 update to the Orange Book does not represent a change in FDA's longstanding position regarding the strength of parenteral solutions; it simply represents the correction of a longstanding error in how strength was displayed for such products.

The well-settled meaning of "strength" as "total drug content" is further confirmed by updates to the United States Pharmacopeia ("USP") implemented during the period leading to enactment of the BPCIA to address the risk of medication errors for parenteral drug products. Indeed, FDA's modernization of the Orange Book in 2003 appears to have been driven, in part, by the same safety concerns that prompted changes to the USP. Prior to 2003, the labeling for many parenteral drugs identified only the concentration (mg/mL) (consistent with Orange Book listings). However, the expression of concentration often was misunderstood by physicians and patients to mean the total drug content of the container. This confusion resulted in dosing errors (*e.g.*, overdoses) and reports of serious adverse events.[22] To address this situation, the USP Safe Medication Use Expert Committee proposed changes to the expression of strength in the labeling of certain parenteral drugs in 2005.[23]

These changes ultimately were approved in 2007 as a new subsection within General Chapter <1> applicable to parenteral drugs, which became official in 2009. This section required labeling to identify the *strength* per total volume as the primary and prominent expression on the principal display panel, followed by the concentration (mg/mL). Strength, in turn, was defined as "total drug content."[24] By this revision, the USP sought to draw clear distinctions between "strength" (total drug content), total volume, and concentration (mg/mL) and to ensure that the actual strength of a parenteral drug product was clearly and prominently identified on its labeling. This revision was proposed and adopted prior to enactment of the BPCIA.

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[22] FDA Drug Safety Communication: Important change to heparin container labels to clearly state the total drug strength (Dec. 6, 2012) (Exhibit 7), *available at* http://wayback.archive-it.org/7993/20170112031647/http://www.fda.gov/Drugs/DrugSafety/ucm330695.htm#background.

[23] *Pharmacopeial Forum (PF)* 31(4) [July-Aug 2005] Volume for Single – and Multiple-Dose Injectable Drug Products; *see also* USP, *White Paper: USP's Role in Patient Safety*, p. 3 (Sept. 23, 2009) (describing history of labeling change proposal) (Exhibit 8).

[24] USP, General Chapter <1>, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products (Vol. 31 2009) (Exhibit 9).

The D.C. Circuit has instructed that "words are to be read in the context in which they are used and in the broader context of the statutory scheme."[25] Consequently, when Congress uses a term of art, courts generally assume that "Congress intended it to have its established meaning."[26] In other words, "[w]hen Congress uses a term with a settled meaning, its intent is clear for purposes of Chevron step one."[27]

This rule applies with special force when Congress borrows language from another statute. According to the Supreme Court, "when administrative and judicial interpretations have settled the meaning of an existing statutory provision, repetition of the same language in a new statute indicates, as a general matter, the intent to incorporate its administrative and judicial interpretations as well."[28] In other words, "if a word is obviously transplanted from another legal source, whether the common law or other legislation, it brings the old soil with it."[29]

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

b. FDA's Current Interpretation of "Strength" Is Foreclosed By the Clear Statutory Text

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

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

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

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

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

[29] *Sekhar v. United States*, 570 U.S. 729, 733 (2013) (citing Justice Frankfurter, Some Reflections on the Reading of Statutes, 47 Colum. L. Rev. 527, 537 (1947)).

FDA is bound by the meaning of unambiguous terms. When Congress referenced "strength" – but not "concentration" – in the BPCIA, it must be presumed to have known the well-established difference between these regulatory concepts and to have acted purposefully in rejecting any "same concentration" requirement for parenteral solutions. As courts have noted, "Congress is presumed to preserve, not abrogate, the background understandings against which it legislates."[30]

Even where Congress has "established an ambiguous line, the agency can go no further than the ambiguity will allow."[31] A "judicial decision concluding that a statutory term admits of *some* ambiguity does not open the door at *Chevron* step one for purposes of *all* interpretations."[32] "[W]here the text and reasonable inferences from it give a clear answer against the government . . . that . . . is the end of the matter" under *Chevron* step one.[33] In other words, "the Court must consider whether the statute 'unambiguously forbids the Agency's interpretation.'"[34] Here, when read in context and using the traditional tools of statutory construction, the BPCIA unambiguously forbids FDA's interpretation of "strength" to mean not just total drug content, but also concentration, for injectable solutions. Even if "strength" were ambiguous in some contexts (*e.g.*, as applied to patches with reservoirs), that does not change its unambiguous meaning in the context of injectable solutions.

The most forceful evidence of this Congressional intent comes from FDA itself. As addressed above, before the BPCIA was enacted, FDA changed the way drug information was listed and labeled in the Orange Book, adding "strength" to the already listed "concentration" to avoid confusion. Orange Book, p. xvii (2009). In the context of parenteral drugs, FDA thus specifically rejected the idea that the "strength" of a parenteral solution encompasses its "concentration," instead treating them as two different, freestanding regulatory concepts.

This distinction between "strength" and "concentration" was further reinforced by several FDA regulations and guidance documents that were operative during the relevant period. For example, FDA regulations governing National Drug Codes ("NDC") required sponsors to obtain a new NDC number if there was any change in "strength or concentration." 21 C.F.R. § 207.35 (2009) (emphasis added). Likewise, the preamble to the 2009 Orange Book defined "pharmaceutical equivalents" to mean drug products that are, *inter alia*, "identical in strength or concentration." Orange Book, p. vii (2009) (emphasis added). FDA's 2004 "bundling guidance" informs sponsors that FDA will accept several "different strengths or concentrations" of a drug

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[30] *Wilson,* 290 F.3d at 356.

[31] *Amarin*, 106 F. Supp. 3d 196, 217 (citing *City of Arlington, Tex. V. FCC*, 569 U.S. 290, 307 (2013)).

[32] *Id.* at 208 (emphasis in original).

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

[34] *Id*. (*citing Barnhart v. Walton*, 535 U.S. 212, 218 (2002)).

product within a single New Drug Application.[35] FDA's bioequivalence regulations also treated "strength" and "concentration" as separate regulatory concepts.[36] Although these references to "strength or concentration" were not specific to parenteral solutions, they reinforce the distinction between "strength" and "concentration" that FDA identified in 2003 when it began listing the "strength" of parenteral solutions in the Orange Book.

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

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

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

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[35] *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, p. 4 (Dec. 2004) (emphasis added).

[36] *Compare* 21 C.F.R. § 320.22(b)(1)(ii) (allowing waiver of *in vivo* bioequivalence testing for parenteral drugs with the same active and inactive ingredients *in the same concentration* as the RLD), *with* 21 C.F.R. § 320.22(d)(2) (allowing waiver of *in vivo* BE testing for *different strengths*).

c. FDA's New Regulation Defining "Strength" Is Irrelevant

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

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

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

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

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

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

[40] *Rouse*, 747 F.3d 707, 714.

[41] *See Stat-Trade*, 869 F. Supp. 2d 95, 105 (rejecting new Agency interpretation of statutory term as inconsistent with the clear statutory language).

Second, by its own terms, the regulation does not apply to biological products subject to licensing under the PHS Act. 21 C.F.R. § 314.1(b). Thus, the definition of "strength" set forth in the revised Hatch-Waxman regulations is simply irrelevant to the subject of this petition – biological products seeking BLA approval via the 351(k) pathway.

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

Even if the term "strength" were ambiguous in the context of parenteral solutions (which it is not), FDA's interpretation nevertheless would be impermissible under step two of the *Chevron* test because it is unreasonable. The FDA's interpretation can survive *Chevron* step two only if the Agency provides "a reasonable explanation for how its interpretation serves the statute."[42] Here, FDA's interpretation *subverts* the goals of the BPCIA in at least two ways. First, FDA's interpretation facilitates and encourages anti-competitive evergreening tactics designed to prevent or delay competition from biological products seeking approval under the 351(k) pathway, contrary to the intent of the BPCIA. Second, FDA's interpretation serves to undermine the BPCIA's goal of speeding the development of biosimilar and interchangeable biological products, with no legitimate countervailing regulatory purpose. Because FDA's interpretation undermines the underlying goals of the BPCIA rather than serves them, it is unreasonable under *Chevron* step two.

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

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

Like the Hatch-Waxman Act upon which it was modeled, "the BPCIA was designed to foster both price competition and innovation in the field of biologics."[43] To encourage innovation, the BPCIA provides four- and twelve-year exclusivity periods to RPs. 42 U.S.C. § 262(k)(7). To protect "consumer interests," the BPCIA creates an *abbreviated* approval pathway, much like the generic drug approval pathway under the Hatch-Waxman Act, to encourage the development of lower-cost, safe and effective biological products. *Id*. § 262(k)(1), (2), (4). Thus, one of the primary goals of the BPCIA is to spur competition among biological products and thereby increase access to affordable biological products by patients in the United States. Indeed, "Price Competition" is part of the Act's popular name.

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

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[42] *Braeburn*, 389 F. Supp. 3d 1, 23.

[43] *Genentech, Inc. v. Amgen, Inc*., 2020 U.S. Dist. LEXIS 23311 (D. Del. Feb. 11, 2020); *see also* BPCIA, Pub. L. No. 111-148, § 7001(b) (2010) ("It is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established."); *Amgen*, 877 F.3d 1315, 1320 (noting that the BPCIA and Hatch-Waxman Act have similar goals, including balancing "innovation and price competition").

interpretation allows brand biologic manufacturers to avoid competition from biological products seeking approval via the 351(k) pathway by making insignificant changes to the RP's concentration that have no impact on the therapeutic safety or effectiveness of such products. To state the most extreme example, under the FDA's interpretation, a brand biologic manufacturer could add or remove *a single drop of water* to its product and thereby block approval of a 351(k) application for a competing product. Moreover, this tactic could be employed as soon as a 351(k) application is approved – or even submitted – to delay, prevent the licensure of, or circumvent the effect of a biosimilar or interchangeable designation in the marketplace.

This tactic is particularly damaging to biosimilar and interchangeable biological products because of the high costs and extended time needed to develop such products. In 2009, the Federal Trade Commission ("FTC") estimated that it likely would take eight to ten years to develop a biosimilar medication, with an estimated development cost of between $100 and $200 million.[44] In Boehringer Ingelheim's experience, these estimates are, if anything, conservative. Moreover, the development of biological products under the 351(k) pathway requires substantial fixed costs because of the complex manufacturing processes and controls needed to produce biological products. These costs and timelines differ substantially from those of small-molecule generic drugs, which typically take three to five years to develop and cost between $1 and $5 million.

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

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

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

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[44] FTC, *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, p. iii (June 2009), *available at* Emerging Health Care Issues: Follow-On Biologic Drug Competition: A Federal Trade Commission Report | Federal Trade Commission (ftc.gov).

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

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

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

If FDA interprets strength to mean "total drug content" without regard to concentration, as intended by Congress, these types of evergreening and product-hopping tactics would be much more difficult to accomplish.[47] Because this type of anti-competitive "game-playing" is antithetical to the intent and goals of the BPCIA, FDA's interpretation – which facilitates this new tactic – is unreasonable under step two of the *Chevron* test.

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[45] FDA, Biosimilars Action Plan: Balancing Innovation and Competition, p. 9 (July 2018) (identifying REMS abuse as a problem for development of biosimilar and interchangeable biological products).

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

[47] Interpreting "strength" to mean "total drug content" would not create unexpected evergreening problems with respect to RP exclusivity. The BPCIA contains a list of changes for which exclusivity cannot be granted (*e.g.*, strength, route of administration, indication). 42 U.S.C. § 262(k)(7)(C)(ii)(I). Although the list does not explicitly mention "concentration," FDA could require changes to the concentration of a RP to be implemented via a supplement, as was done with Humira HC. This solution would avoid potential evergreening concerns while simultaneously encouraging robust price competition.

b. <u>FDA's Interpretation Prevents Licensure of Biological Products That Are Biosimilar to or Interchangeable With the RP</u>

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

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

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

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

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

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[48] *See, e.g.*, Comment of Novartis, FDA-2011-D-0611-0020, pp. 13-14 (April 13, 2012); Comment of Teva Pharmaceuticals, p. 4 (April 20, 2012) (impact of concentration differences is "often negligible").

2. Can be "expected to produce the same clinical result as the reference product in any given patient;" and

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

42 U.S.C. §§ 262(k)(2)(A)(i)(I), (k)(4).

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

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

In sum, because FDA's interpretation of "strength" places an artificial and unnecessary limitation on certain products eligible for approval via the 351(k) pathway, it undermines the BPCIA's core goal of encouraging price competition through the timely approval of biosimilar and interchangeable biological products. As such, it is unreasonable under step two of the *Chevron* test.

4. FDA's Interpretation of "Strength" Is Arbitrary and Capricious in Violation of the Administrative Procedure Act (APA)

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

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

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

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

[50] *Bracco Diagnostics*, 963 F. Supp. at 24.

[51] *Id*. at 28.

treats dry powders intended for reconstitution and injection differently than injectable products already in a solution dosage form.

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

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

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

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

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

Moreover, to Boehringer Ingelheim's knowledge, there are no persuasive countervailing regulatory interests that outweigh the above factors. As noted above, any clinical effects of concentration differences would be identified and addressed through the BPCIA's more calibrated approval requirements rather than through a blunt instrument like the definition of strength. Moreover, interpreting "strength" to mean "total drug content" would <u>not</u> create unexpected evergreening problems with respect to RP exclusivity because FDA could take simple, regulatory steps to avoid such problems (see footnote 47). Finally, there would be no negative effect on the post-market safety of affected products since this change in policy would not require any

modifications in how parenteral solutions are labeled or how adverse experiences are reported or handled. On the contrary, parenteral solutions would continue to be labeled with the strength (total drug content), total volume, and concentration per FDA guidance and USP monograph standards.[52] Consequently, the total volume and concentration could continue to be used to identify, report, and assess suspect products for purposes of post-market safety reporting, and other identifiers also would continue to be used to identify the suspect product (*e.g.*, trade name, NDC number, lot number, etc.). *See* 21 C.F.R. 600.80(f)(1); *see also* FDA Form 3500A (2/19). The only difference is that total volume and concentration would no longer be relevant factors in determining the "strength" of a parenteral solution for purposes of section 351(k) of the PHS Act, 42 U.S.C. § 262(k).

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

C. Conclusion

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

III. Environmental Impact

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

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

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[52] *See* FDA, *Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, pp. 10-11 (April 2013); USP36-NF31, General Chapter <7>, "Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products (Labeling of Official Articles) (Exhibit 12).

V. Certification[53]

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

Respectfully submitted,

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Exhibits

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