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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

AbbVie Inc. (AbbVie) respectfully submits this citizen petition (Petition) to the Food and Drug Administration (FDA) under 21 C.F.R. §§ 10.25 and 10.30, sections 201(n) and 502(a) of the Federal Food, Drug, and Cosmetic Act (FDCA), section 351 of the Public Health Service Act (PHSA), as amended by the Biologics Price Competition and Innovation Act of 2009 (BPCIA), and sections 4(e) and 10 of the Administrative Procedure Act (APA).

I. ACTION REQUESTED

This Petition requests that FDA require that the approved prescription drug labeling for biological products licensed under section 351(k) of the PHSA contain:

(a) A clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all the reference product's conditions of use (if applicable), and that the biosimilar's licensed conditions of use were based on extrapolation (if applicable);

(b) A clear statement that FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and

(c) A concise description of the pertinent data developed to support licensure of the biosimilar, along with information adequate to enable prescribers to distinguish data derived from studies of the biosimilar from data derived from studies of the reference product.

Biosimilars are not generic drugs and should not be labeled like generic drugs. Including the above information in biosimilar labeling is necessary to enable rational and informed prescribing decisions regarding these complex products, to avoid potentially unsafe substitution of biosimilars and reference products, and to combat widespread misconceptions among prescribers about biosimilars and their relationship to reference products. Without this information, biosimilar labeling will not reflect the unique licensure provisions established by the BPCIA and will be materially misleading in violation of the FDCA and FDA regulations. Moreover, FDA proposed in 2012 to include similar information in biosimilar labeling, but recently reversed its position without providing any explanation. The Agency's unexplained about-face on this important public health issue is a violation of the APA.

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II. BACKGROUND

The BPCIA amended section 351 of the PHSA to create a two-tiered abbreviated licensure pathway for follow-on biological products. A biological product can be licensed under the BPCIA if it is "biosimilar" to a "reference product" as set out in section 351(i)(2). Separately, a biosimilar can be deemed "interchangeable" with the reference product if certain heightened showings required by section 351(k)(4) have been made.

To date, FDA's efforts to implement the BPCIA generally have focused on issuing guidance regarding the new statutory standards. FDA began releasing draft guidance documents for public comment in February 2012. In the draft entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" (Draft Scientific Guidance), FDA stated that biosimilar labeling should disclose that the product is a biosimilar, the scope of its approval, and whether it has been found to be interchangeable. According to the Draft Scientific Guidance, including this information in labeling is "necessary" to enable informed prescribing and adequate postmarket safety monitoring.[1] When the guidance was finalized at the end of April 2015 (Final Scientific Guidance), however, it made no mention of biosimilar labeling or the need for biosimilar labeling to provide this information.[2]

On March 6, 2015, while the Draft Scientific Guidance was pending, FDA approved the first biosimilar product in the United States. Zarxio® (filgrastim-sndz), developed by Sandoz Inc., is biosimilar to the reference biological product Neupogen® (filgrastim), which was developed by Amgen, Inc.[3] Zarxio has not been found interchangeable with Neupogen, and the approved labeling for Zarxio does not include the information that FDA had identified as "necessary" in the Draft Scientific Guidance. Instead, the labeling for Zarxio mimics the approved labeling for Neupogen, which suggests that FDA has decided to apply the "same labeling" requirement found in FDCA section 505(j) for small-molecule generic drugs to biosimilars licensed under section 351(k) of the PHSA.

Publicly available materials from FDA's review of Zarxio confirm that FDA followed a "same labeling" approach. According to the action package for Zarxio, in November 2013, Sandoz proposed and FDA agreed that the biosimilar and reference product labeling "should be essentially the same."[4] In February 2015, FDA provided the labeling for Neupogen to Sandoz for use "as a template" in developing the labeling for Zarxio, and instructed Sandoz to track any changes made to the Neupogen labeling and provide annotations to explain and justify any such changes.[5] That is essentially what FDA regulations

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[1] FDA, Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 20-21 (Feb. 2012).

[2] FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 22 (Apr. 2015), http://1.usa.gov/1A4LOLA.

[3] Filgrastim is a granulocyte colony-stimulating factor (G-CSF), a glycoprotein used in a variety of treatment settings, including assisting patients to recover from neutropenia after chemotherapy.

[4] Minutes of Meeting Held November 19, 2013, 16-17 (Dec. 19, 2013), http://1.usa.gov/1G6mYf7; Preliminary Meeting Comments, 13 (Nov. 14, 2013), http://1.usa.gov/1G6mYf7.

[5] Ltr. from Ann T. Farrell, M.D., to John M. Pakulski, R.Ph, 6 (Feb. 6, 2015), http://1.usa.gov/1G6mYf7.

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require of applicants seeking to market generic drugs under section 505(j).[6] Indeed, in the media briefing announcing the approval of Zarxio, the Director of the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) acknowledged that the "approach" taken with respect to the labeling for Zarxio was "not that different from the approach . . . taken in the past . . . for generic applications."[7] Consistent with that approach, the approved labeling for Zarxio is nearly identical to that of Neupogen, as shown in Exhibit A accompanying the Petition.

It would be legally unsound for FDA to adopt a "same labeling" approach to biosimilars, as the Agency has done with respect to Zarxio. First, a "same labeling" approach is flatly inconsistent with the BPCIA, which—unlike the Abbreviated New Drug Application (ANDA) provisions in section 505(j)—includes no "same labeling" requirement and recognizes that biosimilars are different from their reference products (infra § III.A). Second, a "same labeling" approach to biosimilars would result in labeling that omits material information necessary for safe and informed prescribing, and would exacerbate, rather than dispel, misconceptions among prescribers regarding biosimilars (infra § III.B). Finally, FDA has not provided the reasoned explanation required by the APA for its decision to abandon the approach taken in the Draft Scientific Guidance, which stated that the labeling of a biosimilar product should disclose that the product is a biosimilar, the scope of its approval, and whether it has been found to be interchangeable, on the ground that this information is "necessary" for informed prescribing (infra § III.C). For all of these reasons, as discussed below, FDA should take the actions requested in this Petition.

III. STATEMENT OF GROUNDS

A. The "Same Labeling" Requirement That Applies To Generic Drugs Does Not Exist In, And Is Contrary To, The BPCIA.

FDA's apparent decision to apply a "same labeling" requirement to biosimilars is inconsistent with the BPCIA. Congress established a distinct approval pathway for biosimilars, and that pathway includes no analogue to the same labeling requirement that exists for small-molecule generic drugs under the ANDA provisions of the FDCA.

Under section 505(j), an ANDA must contain information to show, among other things, that a proposed generic drug's active ingredient is "the same as" that of the reference listed drug (RLD).[8] The ANDA also must contain information to show, subject to a few exceptions not relevant here, that the proposed labeling for the generic drug is "the same as" the labeling for the RLD.[9] FDA cannot approve

[6] 21 C.F.R. § 314.94(a)(8)(iv) (abbreviated new drug applications must contain a "side-by-side comparison" of the proposed generic and reference product labeling that shows "all differences annotated and explained").

[7] FDA Media Briefing, First Biosimilar Approval in the United States, 6 (Mar. 6, 2015) (statement of Dr. John Jenkins), http://1.usa.gov/1KRJ4Bm.

[8] 21 U.S.C. § 355(j)(2)(A)(ii)(I) (emphasis added); see id. § 355(j)(2)(A)(ii)(II) (same).

[9] Id. § 355(j)(2)(A)(v) (emphasis added).

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an ANDA unless these sameness standards are met,[10] which is why the United States Supreme Court has stated on at least three occasions that a generic drug and its RLD are "the same."[11]

FDA has acknowledged that the 505(j) pathway "is predicated on a finding of the 'same' active ingredient" and, therefore, "will not ordinarily be available" for biological products.[12] As the current Director of CDER told Congress during consideration of the BPCIA, "there is general recognition that the idea of sameness, as the term is used in the generic drug approval process . . . and applied to small molecules, will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products."[13] Consequently, it is "impossible to demonstrate that [a follow-on biological product] is identical to" a previously approved product.[14] The BPCIA pathway therefore does not require a showing that biosimilars are the same as their referents. Instead, biosimilars may be licensed if they are shown to be "sufficiently similar to products already on the market."[15]

Significant public health considerations flow from the fact that biosimilars are not the same as their reference products. In particular, increased risks of immunogenicity can arise if patients are sequentially or repeatedly exposed to similar, but not identical, biological products. Immunogenic responses "can be extremely serious or life-threatening"; examples include "hypersensitivity reactions such as anaphylaxis, rash, fever and kidney problems," as well as potential cross-reactions with endogenous proteins.[16] Immunogenic responses also can have a significant impact on effectiveness, "including the potential to decrease or block the clinical effect."[17] For these reasons, an accurate "assessment of immunogenicity" is "critical" when evaluating all biological products, including biosimilars.[18] At FDA's urging, Congress addressed these risks by requiring more from biosimilar

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[10] Id. § 355(j)(4)(G); 21 C.F.R. § 314.127(a)(7).

[11] Mutual Pharm. Co. v. Bartlett, 133 S. Ct. 2466, 2475 (2013); Pliva v. Mensing, 131 S. Ct. 2567, 2584 (2011); Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990).

[12] FDA, Citizen Petition Resp., Docket No. FDA-2009-P-0004, 4 (Feb. 24, 2012).

[13] Follow-on Protein Products, Statement of Janet Woodcock, M.D., before the H. Comm. on Oversight and Gov't Reform (Mar. 26, 2007), http://1.usa.gov/1ImtEHI (First Woodcock Statement).

[14] Celltrion Healthcare Co., Ltd. v. Kennedy Trust for Rheumatology Research, No. 14-2256, 2014 U.S. Dist. LEXIS 166491, at *4 n.1 (S.D.N.Y. Dec. 1, 2014); accord Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States, Statement of Janet Woodcock, M.D., before the Subcomm. on Health, H. Comm. On Energy and Commerce (May 2, 2007), http://1.usa.gov/1FIGxrU ("Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product.") (Second Woodcock Statement).

[15] Amgen Inc. v. Sandoz Inc., No. 14-4741, 2015 U.S. Dist. LEXIS 34537, at *2-3 (N.D. Cal. Mar. 19, 2015) (emphasis added); accord Sandoz Inc. v. Amgen Inc., No. 13-2094, 2013 U.S. Dist. LEXIS 161233, at *3 n.1 (N.D. Cal. Nov. 12, 2013) ("A biosimilar is a drug product designed to be similar to a previously approved biologic drug . . . in its quality, safety, and efficacy.").

[16] First Woodcock Statement.

[17] Ltr. from Frank M. Torti, M.D. to Frank Pallone, Jr., 1 (Sept. 18, 2008) (Torti Letter).

[18] Id. at 2.

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applicants than is required from ANDA applicants. Most ANDAs require only in-vitro and limited clinical bioequivalence studies,[19] but the BPCIA requires biosimilar applications to include immunogenicity data from a clinical study or studies.[20]

To be sure, the BPCIA does borrow some provisions from the ANDA pathway, but Congress' decision not to borrow the same labeling requirement makes clear that FDA cannot follow that approach to biosimilar labeling. Under the BPCIA, a biosimilar applicant must seek approval for "conditions of use" that were "previously approved for the reference product," and must show that the "route of administration, the dosage form, and the strength" of the biosimilar are "the same as those of the reference product."[21] Those requirements are directly analogous to ANDA requirements.[22] The BPCIA does not, however, contain anything comparable to the 505(j) same labeling requirement.[23]

In other words, Congress chose to include in the BPCIA some provisions from section 505(j) and to exclude other ANDA requirements. Under settled rules of statutory construction, Congress is presumed to have acted "'intentionally and purposely in the disparate inclusion or exclusion.'"[24] Indeed, FDA previously concluded that Congress acted intentionally when it omitted the same labeling requirement from section 505(b)(2) of the FDCA. As FDA put it, there are "no analogues in section 505(b)(2) to the provisions in section 505(j) requiring that the product . . . use the same labeling."[25] "No such sameness requirement was included" in 505(b)(2) because, according to the Agency, Congress did not intend for section 505(b)(2) to be limited to just duplicate products.[26] The same principle applies here. The BPCIA includes "no such sameness requirement" because biosimilars are not duplicates of their reference products.

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[19] See 21 U.S.C. § 355(j)(7)(A)(III).

[20] 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc). FDA may waive that requirement. See id. § 262(k)(2)(A)(ii); cf. Torti Letter at 2 ("We believe that such studies must be mandated in statute, while allowing FDA the discretion to determine how much data are necessary for the assessment of immunogenicity.").

[21] 42 U.S.C. § 262(k)(2)(A)(iii)-(iv).

[22] See 21 U.S.C. § 355(j)(2)(A)(i), (iii).

[23] See id. § 355(j)(2)(A)(v), 355(j)(4)(G).

[24] Gozlon-Peretz v. United States, 498 U.S. 395, 404 (1991) (quoting Russello v. United States, 464 U.S. 16, 23 (1983)); accord Gross v. FBL Financial Services, Inc., 557 U.S. 167, 174-75 (2009) (Congress's inclusion of a particular standard in Title VII of the Civil Rights Act, but not the Age Discrimination in Employment Act, gave rise to a "negative implication" that the omission was intentional); Custis v. United States, 511 U.S. 485, 491-92 (1994) ("Congress' omission of similar language" from "other related statutes" shows that Congress "did not intend" for the omitted condition to apply). The fact that the PHSA and FDCA cross-reference each other, and the fact that Congress amended both statutes through the BPCIA, strengthens the conclusion that Congress acted intentionally in adopting some, but not all, of the ANDA requirements for biosimilars. See Lindh v. Murphy, 521 U.S. 320, 330 (1997) ("[N]egative implications raised by disparate provisions are strongest when the portions of a statute treated differently had already been joined together and were being considered simultaneously when the language raising the implication was inserted").

[25] FDA, Citizen Petition Resp., Docket Nos. 2001P-0323, 2002P-0447, 2003P-0408, 18 (Oct. 14, 2003).

[26] Id. ("If 505(b)(2) applications were limited to literature-based duplicates, surely Congress would have required that, like those approved in ANDAs, products approved in 505(b)(2) applications . . . [have] the same labeling").

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Another crucial distinction between the BPCIA and 505(j) pertains to therapeutic equivalence. The same labeling requirement reflects the fact that ANDA drugs generally are therapeutically equivalent to, and substitutable for, their respective RLDs.[27] Even when FDA exempts an ANDA drug from the same labeling requirement, FDA usually specifies that the drug is substitutable for the RLD.[28] As FDA has explained, the concept of therapeutic equivalence applies "to drug products containing the same active ingredients," but does not encompass "different therapeutic agents."[29]

A non-interchangeable biosimilar is a "different therapeutic agent" from its reference product as a matter of law. Congress, as part of the BPCIA, amended section 505A of the FDCA, the Pediatric Research Equity Act (PREA), to state that a non-interchangeable biosimilar is "a new active ingredient" for purposes of pediatric research, but an interchangeable product is not.[30] The sponsor of a non-interchangeable biosimilar therefore must conduct pediatric assessments unless that requirement is deferred or waived by FDA.[31] Congress's decision to subject biosimilars to the PREA—which does not apply at all to ANDA drugs[32]—underscores that Congress was aware that biosimilars differ from their reference products, unlike generic drugs in the ANDA context.

In sum, the characterizing feature of the BPCIA pathway is that it deems biosimilars to be different from their referents, which distinguishes the BPCIA from the FDCA's ANDA provisions. Applying the same labeling requirement for ANDA products to biosimilars would conflict with the novel licensing scheme established by the BPCIA. The same labeling approach in this context is therefore legally unsound, and FDA should not use this approach in reviewing the labeling for products submitted for review under the BPCIA.

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[27] See 21 U.S.C. § 355(j)(2)(A)(iv), 355(j)(4)(F); see also Hill Dermaceuticals, Inc. v. FDA, 826 F. Supp. 2d 252, 261 (D.D.C. 2011) ("pharmacists will substitute the generic product for the brand-name drug—and are often required to substitute generic products under state law"). A limited exception exists for ANDAs submitted pursuant to suitability petitions. See 21 C.F.R. § 314.93(b).

[28] See, e.g., FDA, Citizen Petition Resp., Docket Nos. 01P-0495, 02P-0191, 02P-0252, 13 (June 11, 2002) ("omission of information protected by exclusivity will not be a basis for altering a therapeutic equivalence rating") (citing 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994)).

[29] FDA, Orange Book Preface (34th Ed., Mar. 14, 2014), http://1.usa.gov/1yPiHIl.

[30] See 21 U.S.C. § 355c(m)(1)-(2).

[31] See id. § 355c(a)(1)(B), (a)(2), (a)(3), (a)(4); see also FDA, Guidance for Industry: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, 13 (Apr. 2015), http://1.usa.gov/1DxTNva ("if an applicant first seeks licensure of its proposed product as a non-interchangeable biosimilar product and intends to subsequently seek licensure of the product as interchangeable, the applicant still must address PREA requirements when it seeks initial licensure") (Final Q&A Guidance).

[32] See, e.g., FDA, Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, 4 (Sept 2005), http://1.usa.gov/1K77ytl ("PREA does not impose pediatric assessment requirements on . . . generic drugs").

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B. Applying A "Same Labeling" Requirement To Biosimilars Leads to Labeling That Is Misleading In Violation Of The FDCA And FDA Regulations.

In addition to conflicting with the BPCIA, a "same labeling" approach to biosimilars would create serious misbranding issues under the FDCA and FDA regulations. Under section 502(a) of the FDCA, a drug is misbranded if its labeling is false or misleading in any particular.[33] Under section 201(n), labeling is misleading if it omits material facts as described in that provision.[34] FDA regulations governing physician labeling likewise prohibit material omissions.[35] As detailed below, a "same labeling" approach to biosimilar labeling violates these basic statutory and regulatory requirements in several respects.

1. Biosimilar Labeling Must Include Information Necessary To Enable Informed Prescribing And To Dispel Common Misconceptions.

The labeling statements requested in this Petition are necessary to enable informed prescribing decisions and to dispel common and widespread misconceptions among prescribers about biosimilars and their relationship to their respective reference products. FDA has long recognized that physician labeling is "the primary source of information about a product" for prescribers.[36] Consistent with section 201(n) of the statute, FDA regulations provide that labeling "shall be deemed to be misleading if it fails to reveal facts that are . . . [m]aterial in light of other representations made or suggested by statement, word, design, device or any combination thereof."[37] Whether an omission is material "is determined by the degree to which [the] information is objectively important, relevant, or substantial to the target audience."[38] In other words, a material fact is one that reasonably would influence "the intended audience."[39]

The intended audience for physician labeling is the health care professional prescribing the drug.[40] FDA has recognized that "[t]he relevant properties of a product" are core material facts that must be disclosed.[41] A recent survey of 400 U.S. board-certified physicians shows definitively that the

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[33] 21 U.S.C. § 352(a).

[34] See id. § 321(n), 352(a); 21 C.F.R. § 201.56(a)(2).

[35] See, e.g., 21 C.F.R. §§ 1.21(a), 201.56(a)(2).

[36] 71 Fed. Reg. 3922, 3964 (Jan. 24, 2006).

[37] 21 C.F.R. § 1.21(a); see 21 U.S.C. § 321(n).

[38] FDA, Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion, 11 (May 2009), http://1.usa.gov/1KWaMwW (Draft Risk Guidance); accord United States v. Watkins, 278 F.3d 961, 967-68 (9th Cir. 2002) (citing Neder v. United States, 527 U.S. 1, 22 n.5 (1999) and Restatement (Second) of Torts § 538(a) (1977)); U.S. Attorney's Manual, Civil Resource Manual § 98, 'Materiality' in FDCA Prosecutions (Nov. 2002), http://1.usa.gov/1cVyIGd.

[39] Draft Risk Guidance at 12.

[40] 71 Fed. Reg. at 3922. When it promulgated the Physician Labeling Rule, FDA "used focus groups" and "a national physician survey" and other tools to determine "what labeling information practitioners consider most important." Id.

[41] E.g., Draft Risk Guidance at 12.

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labeling information at issue in this Petition addresses product properties that are highly relevant, and thus material, to prescribers. Among other things, the survey showed that:

- 90% of prescribers thought it was important "that a product label for a biosimilar clearly indicates that it is a biosimilar";
- 80% of prescribers thought it was important "that the label makes clear which indications were studied by the biosimilar sponsor and which indications were approved based on extrapolation from studies in other indications";
- 79% of prescribers thought it was important "that the label explicitly states that specific indications or conditions of use that are approved for the originator are NOT approved for the biosimilar product";
- 79% of prescribers thought it was important "that a product label clearly indicates a biosimilar is or is not interchangeable";
- 83% of prescribers thought it was important "that the biosimilar label includes the clinical data, if any, submitted to FDA by the biosimilar sponsor";
- 79% of prescribers thought it was important "that the label includes all relevant clinical similarity data, including clinical immunogenicity findings, from the biosimilar product development; and
- 79% of prescribers thought it was important "that the label clearly distinguishes those data generated by the biosimilar sponsor from those generated by the originator sponsor."[42]

These findings are not surprising. As discussed below, prescriber groups have supported requirements for the presentation of this information in biosimilar labeling.[43] The Institute for Patient Access recently criticized FDA's "questionable approach" to the labeling for Zarxio "because . . . physicians need complete and specific information about medications they prescribe."[44] More recently still, "eight groups representing a broad spectrum of physicians who prescribe biologics" responded to FDA's approval of Zarxio by sending a letter to FDA "underscoring the need to ensure that biosimilar product

[42] Kevin Olson, ASBM Labeling Survey (Feb. 2015), http://bit.ly/1dSMeup (ASBM Labeling Survey).

[43] Infra § III.C.

[44] David Charles, M.D. and Mary Ann Chapman, Ph.D., Informed Prescribing: Physicians Need Complete and Specific Prescribing Information for Biosimilar Medications, 1 (May 2015), http://bit.ly/1KNCQCo (Informed Prescribing); id. at 2 (To "ensure transparent" labeling and to "give physicians access to the most accurate and pertinent information," biosimilar labeling "must clearly state that the product is a biosimilar and indicate whether or not it is therapeutically interchangeable with the original biologic. It must also include safety and effectiveness data obtained specifically with the biosimilar. If information generated from the original biologic is included, it should be clearly stated in the document.").

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labeling contains all needed data for physicians to make appropriate prescribing decisions for their patients."[45]

Transparency in biosimilar labeling is needed not only to enable informed prescribing, but also to dispel widespread misconceptions about biosimilar products. Biosimilars are commonly described, even today, as "generic" or "biogeneric" products.[46] As FDA twice told Congress, "[t]hese terms are imprecise and can be confusing" and using them to describe biosimilars "inaccurately implies the same meaning as exists for generic drugs."[47] Survey evidence suggests that similar misconceptions exist among prescribers. For instance, a report published in June 2010 found that 54% of interviewed prescribers in the United States were unaware that the BPCIA pathway existed.[48] A follow-up report published in February 2013 found that 54% of surveyed physicians either "could not define" or had "never heard of" biosimilars.[49] Another follow-up found in June 2014 that 39% of surveyed physicians still could not define or had not heard of biosimilars.[50] Similar survey results have been reported by the National Comprehensive Cancer Network in 2011 and by the North American Center for Continuing

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[45] PR Newswire, Physician Groups Urge FDA to Ensure Patient Safety With Greater Transparency in Biosimilar Labeling: Following Approval of the First Biosimilar in the U.S., Physician Groups Urge FDA to Give Full Consideration to Inclusion of Critical Information Needed by Physicians (May 21, 2015), http://prn.to/1Hl0FOY.

[46] See, e.g., Generic Pharm. Ass'n, Comments to Docket No. FDA-2010-N-0477 (Dec. 30. 2010) (referring to biosimilars as "biogenerics" throughout); Derrick Gingery, Are Potential Biosimilar Sponsors Still Hesitant About The Pathway Despite Expected Growth?, The Pink Sheet (Mar. 4, 2013) ("Just like when Hatch-Waxman was enacted, ideally I would have loved for [FDA] to have a separate office . . . focused on biogeneric approvals") (statement of Tony Mauro, Mylan Inc.); Press Release, Sunshine Biopharma Announces Changes (Feb. 25, 2015), http://mwne.ws/1H9zh6p (describing the "production of biogeneric therapeutic proteins"); see also, e.g., Jonathan Rockoff, FDA Approves First Generic Biotech Drug, Wall Street Journal (Mar. 6, 2015), http://on.wsj.com/1PQIElu; Paul Scolardi, How to Invest in the New Industry of 'Biosimilar' or 'Generic' Biological Drugs, TheStreet.com (Jan. 9, 2015), http://bit.ly/1Ec42We; Sabrina Tavernise, For First Time, FDA Panel Approves Generic Copy of Costly Biologic Drug, New York Times (Jan. 7, 2015), http://nyti.ms/1J9zISS; Tr. of the John King Show, CNN (May 8, 2012), http://bit.ly/1PNlEi5 ("people . . . are now going to see what we call generic biologics on the market").

[47] First Woodcock Statement; Second Woodcock Statement. In other contexts, FDA also has indicated that it is misleading to use the word "generic" to describe products not approved under section 505(j). See FDA, FDA Basics—What are unapproved drugs and why are they on the market? (Jan. 4, 2011), http://1.usa.gov/1JQalEb ("[S]ince many unapproved drugs are marketed without brand names and have been available for many years, it is often assumed that these unapproved drugs are generic drugs. This is not correct. Generic drugs have been evaluated and approved by FDA to demonstrate bioequivalence to a brand name reference drug. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same quality, strength, purity and stability as brand name drugs. Additionally, the generic manufacturing, packaging, and testing sites must meet the same quality standards as those of brand name drugs.").

[48] See Industry Standard Research, Biosimilar Prescribing Outlook, 16 (June 2010), http://bit.ly/1Jd3FkQ.

[49] Industry Standard Research, Biosimilar Primer: US Primary Care Physicians' Attitudes, Beliefs, and Intentions, 8 (Feb. 2013), http://bit.ly/1FSsiSS.

[50] Industry Standard Research, Biosimilar Primer: US Primary Care Physicians' Attitudes, Beliefs, and Intentions, 12 (June 2014), http://bit.ly/1FJ7g84.

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Medical Education in 2013.[51] Indeed, it is questionable whether any prescribers beyond those most familiar with FDA's various pre-market review pathways currently appreciate the significant differences among generic drugs, RLDs, biosimilars, interchangeable biosimilars, and reference products. Unsurprisingly, FDA officials have recognized that public education on these issues is an important priority.[52]

A "same labeling" approach to biosimilars is at odds with that priority and will instead deepen existing misconceptions. "Given the level of education that still needs to take place surrounding biosimilars, some physicians may mistakenly view that an identical label implies that a biosimilar is interchangeable with the reference product and has approval for all of the same indications—which we know may not be the case for many biosimilars."[53] That result would be contrary to the notion, reflected in FDA regulations, that prescription drug labeling should both affirmatively present safety and effectiveness information needed for informed prescribing, and rebut or dispel commonly held misconceptions.[54] Given the novelty of the abbreviated licensure provisions included in the BPCIA, and the broad familiarity with generic drugs authorized under the ANDA pathway, FDA must ensure that biosimilar labeling provides prescribers with the information they need to understand the important differences between these products.

2. Prescribers Need To Know Whether A Product Is A Biosimilar And The Nature And Scope Of Its Approval.

The clearest and simplest facts that should be disclosed in the labeling for any biosimilar pertain to its approval status. Zarxio was approved, as FDA put it, based on "less than a full complement of product-specific preclinical and clinical data."[55] More specifically, the "pivotal" clinical program for Zarxio was designed to show its "non-inferiority" in the prophylaxis of neutropenia in breast cancer

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[51] See Andrew D. Zelenetz, et al., NCCN Biosimilars White Paper: Regulatory, Scientific, and Patient Safety Perspectives, 9(4) J. NCCN S-1, S-15 (Sept. 2011), http://bit.ly/1G8V0AV; Stephen Chavez, CME Survey Biosimilars (May 24, 2013), http://bit.ly/1Jd5K0k. Similar results also were reported in Europe in November 2013, where biosimilars have been marketed since 2006—approximately 24% of European prescribers remain unfamiliar with biosimilars and 37% remain unaware that biosimilar approvals are generally based on an extrapolation of indications rather than direct evidence of safety and effectiveness. See Kevin Olson, ASBM European Prescribers Survey, 11 (Nov. 2013), http://bit.ly/1EH8EW5.

[52] See, e.g., Mari Serebrov, Don't Call Them Generics, Bio World Perspectives (Jan. 29, 2013), http://bit.ly/19Dvghr ("FDA's Rachel Sherman said the biggest challenge the agency faces with biosimilars is educating the public. . . . Her worst nightmare would be for a formulary, seeing a big price difference, to treat biosimilars as it would a generic and switch everyone from the reference biologic to the biosimilar, regardless of the indication."); M. Nielsen Hobbs, Biosimilar Guidances Expected in the 'Near Future,' But Unnecessary, FDA Says, The Pink Sheet Daily (Dec. 4, 2014) ("FDA efforts include 'consumer and patient education and outreach, education and outreach for the practitioners . . . . We intend to continue that after the applications are approved.'") (quoting Sally Howard, Deputy Commissioner for Policy, Planning, Legislation and Analysis).

[53] Ltr. to S. Ostroff from the Alliance for Patient Access, et al. (May 21, 2015), http://bit.ly/1J2xKnl.

[54] Cf. 21 C.F.R. § 201.57(c)(2)(ii); 71 Fed. Reg. at 3944; 44 Fed. Reg. 37434, 37446 (1979).

[55] FDA, FDA approves first biosimilar product Zarxio (Mar. 6, 2015), http://1.usa.gov/1IL85R0.

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patients undergoing chemotherapy, as well as a PK/PD study in healthy volunteers.[56] The other five indications for which Zarxio was licensed were extrapolated based on the breast cancer trials and other supportive data.[57] In addition, the reference product was licensed for a new indication after Zarxio was approved.[58] None of these facts can be divined from the approved labeling for Zarxio.

Such omissions result in materially misleading biosimilar labeling. In the preamble accompanying the physician labeling draft rule, FDA stated that "the basis for approval of the drug product, including the extent of the product's benefits," should be included in labeling "to provide practitioners with more accurate and specific information about a drug's efficacy that could help them to make informed prescribing decisions."[59] Thus, FDA regulations provide for the basis for a drug's approval to be disclosed in its approved physician labeling. For example, for drugs (including biological products) that are approved on the basis of surrogate endpoint data,[60] FDA regulations require that the labeling: (1) disclose that the approval was based on studies using surrogate endpoints; (2) provide "a succinct description" of any limitations or uncertainties about the product; and (3) refer to a full "discussion of the available evidence" elsewhere in the labeling.[61] These labeling statements are, in FDA's words, "necessary to ensure that the information in labeling regarding a drug product's indications or uses is not misleading."[62]

Similarly, some drugs and biological products are approved based solely on animal testing because human testing would be unethical.[63] FDA has stated that labeling for products so approved "would be misleading if information were not included to explain to patients or potential patients that the effectiveness of the product was demonstrated in animals not humans."[64] FDA's regulations therefore require the labeling for such products to state that their approval is based on efficacy studies conducted in animals.[65] Neupogen is such a drug, and its labeling states both that efficacy studies "could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons"

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[56] Sandoz, Advisory Committee Brief, 53 (Jan. 7, 2015), http://1.usa.gov/1xBJx6L (Sandoz Brief).

[57] See id. at 23-24; 51.

[58] Ltr. from Libero L. Marzella to Janet Chow, at 1 (Mar. 30, 2015), http://1.usa.gov/1Ji1ixy ("to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome").

[59] 65 Fed. Reg. 81082, 81095 (Dec. 22, 2000).

[60] See 21 C.F.R. §§ 314.510, 601.41.

[61] Id. § 201.57(c)(2)(i)(B); see FDA, Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway, at 3 (Mar. 2014), http://1.usa.gov/1l0nPlb.

[62] 65 Fed. Reg. 81082, 81098-99 (Dec. 22, 2000) (preamble for proposed Physician Labeling Rule; proposing "broad and prompt" implementation of the provisions now found at § 201.57(c)(2)(i) because they were among the changes necessary to avoid misleading labeling).

[63] See 21 C.F.R., Part 314, Subpart I; 21 C.F.R., Part 601, Subpart H.

[64] 67 Fed. Reg. 37988, 37992 (May 31, 2002) (citing section 502(a) of the FDCA).

[65] See 21 C.F.R. §§ 314.610(b)(3), 601.91(b)(3).

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and that FDA's decision to approve Neupogen for use in patients acutely exposed to myelosuppressive doses of radiation "was based on efficacy studies conducted in animals and data supporting . . . other approved indications."[66]

A third example involves pediatric use. In appropriate cases, "pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies."[67] When pediatric effectiveness has been extrapolated from studies in adults, the physician labeling for the drug must contain an explicit statement that this has occurred, and it also must include "wording that accurately describes the data submitted."[68]

The same approach is required for biosimilar labeling. Just as prescribers need to be informed when a biological product is approved under special pathways using surrogate endpoint or animal efficacy data, prescribers also should be informed when a biological product has been approved as a biosimilar based on similarly limited data presentations. Just as prescribers need to know when pediatric efficacy was based on extrapolation, they should be informed when biosimilar licensure relied on the extrapolation of indications. In all such cases, clear information describing the basis for FDA's finding of efficacy is calculated to facilitate informed prescribing because prescribers would ordinarily assume that approval is based on a familiar package of data and information. The novelty of the biosimilar pathway makes it highly unlikely, if not impossible, that prescribers are aware of the approval standards applicable in that context. Moreover, as shown above, the basis of FDA's approval is information that prescribers find material: 90% of prescribers wish to know whether a product is a biosimilar, 70% wish to know whether the biosimilar was licensed for all of the reference product's conditions of use, and 80% wish to know which conditions of use were licensed based on extrapolation.[69]

The need for this information will only increase as biosimilars of a single reference product become available from multiple sources, as contemplated by the BPCIA.[70] The statute allows each applicant to customize the presentations and conditions of use for which their biosimilar is licensed.[71] Over time, this is likely to lead to an environment in which prescribers must choose among the reference product and multiple biosimilars that have been licensed for different subsets of the reference product's approved presentations and conditions of use. Yet, the approach to biosimilar labeling that FDA appears to have adopted would result in nearly identical labeling for all of those products, as in the ANDA context.

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[66] Neupogen Package Insert, § 14.6 (Mar. 2015), http://bit.ly/1s2wMyt.

[67] 21 U.S.C. § 355c(a)(2)(B)(i) (emphasis added).

[68] 21 C.F.R. § 201.57(c)(9)(iv)(D)(1).

[69] ASBM Labeling Survey.

[70] See 42 U.S.C. § 262(k)(1) ("[a]ny person may submit" a biosimilar application).

[71] See id. § 262(k)(2)(A)(i)(I)(cc); see also Final Q&A Guidance at 7-8.

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Other jurisdictions require biosimilar labeling to include the information at issue in this Petition.[72] The European labeling for Zarzio and other biosimilars states that it is "a biosimilar medicinal product" and directs the reader to the EMA website for more information.[73] Existing guidance in New Zealand likewise provides for biosimilar labeling to include a statement that the product is a biosimilar and not a generic drug.[74] Guidance from Health Canada states that, "[u]nlike generic pharmaceutical drugs, the sponsor of a [biosimilar] will not be able to utilize the [labeling] of the reference biologic drug in its entirety as that of its own product."[75] Health Canada therefore states that the labeling for the biosimilar will include, among other things, "a statement indicating that the product is [a biosimilar]," information regarding "the indications approved for use," and the "data on which the decision for market authorization was made."[76] Thus, the Canadian monograph for Remsima® (infliximab) states that it is "a subsequent entry biologic product" and was approved based on a showing of "similarity" or "comparability" through comparative studies "in patients with rheumatoid arthritis or ankylosing spondylitis" and that other indications were "granted on the basis of similarity."[77]

Similar information should be provided to prescribers in the United States. Physicians need and want to know whether a product is a biosimilar, the scope of its approval, and whether the approval was based on extrapolation. Indeed, FDA itself proposed to require labeling statements of this type in 2012. The Draft Scientific Guidance stated that biosimilar labeling "should include all the information necessary for a health professional to make prescribing decisions."[78] According to the draft, the "necessary" information included "a clear statement" advising that the "product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s)."[79] As discussed below (§ III.C), FDA's decision to chart a different course with Zarxio, and its subsequent revision of the guidance, has not been explained.

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[72] FDA regularly takes note of the actions of other national or international regulatory authorities," even though "those actions do not constrain [its] decision-making." FDA, Citizen Petition Resp., Docket No. FDA-2003-P-0273 (July 23, 2010). Indeed, FDA has established an international "biosimilars cluster" with the European Medicines Agency (EMA) and Health Canada. See Generics and Biosimilars Initiative (GaBi), EMA and FDA report on collaborative efforts (May 16, 2014), http://bit.ly/1RVpSIr.

[73] Zarzio® (filgrastim) Summary of Product Characteristics, § 5.1, http://bit.ly/1Ab8SYN. An identical statement is found in the European labeling for Tevagrastim® (another biosimilar of filgrastim), Omnitrope® (biosimilar somatropin), Remsima® and Inflectra® (both biosimilar infliximab), and Binocrit® (biosimilar epoetin alfa).

[74] New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE), Medicines—Biosimilars (May 2, 2014), http://bit.ly/1FqRHF3 (New Zealand Biosimilar Guidance).

[75] Health Canada, Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs), § 2.5 (Mar. 5, 2010), http://bit.ly/1PqCLLM (Canada Biosimilar Guidance).

[76] Id.

[77] Remsima® (infliximab), Product Monograph, 3 (Mar. 31, 2014), http://bit.ly/1c9dL9l.

[78] Draft Scientific Guidance at 21.

[79] Id.

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3. Prescribers Need To Know Whether A Biosimilar Is Interchangeable With The Reference Product.

The "same labeling" approach is especially problematic when applied to biosimilars that, like Zarxio, have not been determined to be interchangeable under PHSA section 351(k)(4). As discussed above (§ III.A), the BPCIA distinguishes between interchangeable and non-interchangeable biosimilars, and that distinction has real-world consequences for prescribers, pharmacists, and patients. Non-interchangeable biosimilars have not been shown to be therapeutically equivalent to their reference products and, therefore, should not be substituted for their reference products. On the other hand, an interchangeable biosimilar could be substituted for its reference product under applicable state pharmacy laws.

Absent information in a biosimilar's labeling describing its "interchangeability" status, prescribers may not be able to tell whether the biosimilar is a potential substitute for the reference product. Omitting that information misleadingly suggests that the biosimilar could be substituted for its referent, just like a generic drug, which increases the risk of inappropriate product switching.

FDA previously stated that this result—substitution of non-interchangeable biological products—was unacceptable. Thus, the Agency's position paper in September 2006 for the World Health Organization noted the need for "mechanisms" to prevent "potentially dangerous substitutions" and to ensure that "potentially unsafe drug dispensing decisions are not made" due to a "misperception . . . [of] interchangeability."[80] The Agency further explained that one of the "recognized mechanisms" for mitigating those risks was "specific labeling regarding pharmacologic interchangeability."[81] Six months later, the current CDER Director twice testified before Congress that the potential "for repeated switches" between biosimilar and reference biological products carries a significant risk in terms of both safety and effectiveness.[82] Around the same time, a group of fifteen senior FDA officials published a position paper reiterating that inappropriate switching between "complex proteins" poses significant risks to patients.[83] A year later, the Deputy Commissioner informed Congress that "FDA's paramount concern" during consideration of the BPCIA was "that patients not be exposed to an avoidable safety risk by being switched to a product not known to be interchangeable with the product they are currently receiving."[84] And, in 2013, a senior FDA official stated that the Agency's "worst nightmare" would be for biosimilars to be treated as substitutable generics.[85]

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[80] FDA, Discussions by National Regulatory Authorities with World Health Organization on Possible International Non-proprietary Name Policies for Biosimilars (Sept. 1, 2006), http://1.usa.gov/19chqCr (WHO Policy Paper).

[81] Id. (emphasis added).

[82] First Woodcock Statement; Second Woodcock Statement.

[83] Robert Temple, M.D., et al., The FDA's assessment of follow-on protein products: a historical perspective, 6 Nature Reviews 437, 440 (June 2007).

[84] Torti Letter at 3 (Sept. 18, 2008).

[85] Mari Serebrov, Don't Call Them Generics, Bio World Perspectives (Jan. 29, 2013), http://bit.ly/19Dvghr (statement of Rachel Sherman).

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Other regulators have taken steps to address this issue. Current biosimilar guidance from Health Canada states that "there should be no claims" in product labeling that a biosimilar is either bioequivalent or clinically equivalent to the reference product.[86] Current guidance from MEDSAFE New Zealand states that biosimilar labeling should include a clear statement regarding interchangeability status and "a statement that the prescribing physician should be involved in any decision regarding interchangeability."[87]

FDA also appeared to take steps to prevent inappropriate substitution, at least prior to the Zarxio approval. The Draft Scientific Guidance stated that biosimilar labeling should "clearly state . . . whether or not it is therapeutically interchangeable with the original biologic."[88] Such a "clear statement" regarding interchangeability was one of the postmarketing safety measures included to mitigate the "[r]are, but potentially serious, safety risks (e.g., immunogenicity) [that] may not be detected during preapproval clinical testing."[89] It is a mystery how FDA could later determine when it issued the Final Scientific Guidance that interchangeability status is no longer material information for prescribers. Indeed, as several members of the United States Senate Committee on Health, Education, Labor, and Pensions recently explained, omitting that information from biosimilar labeling can only lead to more uncertainty.[90]

4. Prescribers Need Biosimilar-Specific Data And Also Need To Know Whether Data Discussed In Labeling Are From The Biosimilar Or From The Reference Product.

Labeling a biosimilar the same as its reference product distorts the safety and efficacy profile of the biosimilar in at least two ways—it omits important safety and efficacy data from studies of the biosimilar while also concealing the fact that the data that are presented in the labeling were derived from studies of the reference product. "[A] biosimilar—unlike a generic small molecule—has its own clinical data," and those data "will help physicians" by providing information that might "vary from the reference biologic."[91] A "same labeling" approach suppresses that vital information, which health care professionals need to safely prescribe biosimilars.

The labeling for Zarxio illustrates the problem. The first subsection of the "Clinical Studies" section addresses "Patients with Cancer Receiving Myelosuppressive Chemotherapy" and describes a reference product study in patients with small cell lung cancer. But the labeling does not disclose that the study involved Neupogen, or that Zarxio was not actually studied in patients with lung cancer. At the same time, the labeling fails to disclose that Sandoz did conduct a pivotal trial (EP06-302) in patients with breast cancer that compared Zarxio and Neupogen using a non-inferiority design. In other words,

[86] Canada Biosimilar Guidance § 2.5.

[87] New Zealand Biosimilar Guidance.

[88] Draft Scientific Guidance at 21.

[89] Id. at 20-21.

[90] See Ltr. to S. Ostroff from L. Alexander et al., at 2 (Apr. 30, 2015), http://1.usa.gov/1cC5Hi2.

[91] Ltr. to S. Ostroff from the Alliance for Patient Access, et al. (May 21, 2015), http://bit.ly/1J2xKnl.

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efficacy of Neupogen was established in a study in patients with lung cancer, and the non-inferiority of Zarxio was established in patients with breast cancer. FDA's own regulations and guidance recognize that this kind of information needs to be included in prescription drug labeling.[92] Yet it is nowhere to be found in the labeling for Zarxio.

These types of failures do not just result in material omissions; they also result in affirmative misrepresentations. For example, Section 2.3 of the Zarxio labeling addresses dosing in patients undergoing autologous peripheral blood progenitor cell collection and therapy. A comparison of the reference product and biosimilar labeling indicates that the following substitution was made:

Administer **NEUPOGEN** for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of **Neupogen** administration and leukapheresis schedule have not been established, administration of **filgrastim** for 6 to 7 days with leukapheresis on days 5, 6, and 7 was found to be safe and effective [see Clinical Studies (14.4)].	Administer **ZARXIO** for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of **ZARXIO** administration and leukapheresis schedule have not been established, administration of **filgrastim** for 6 to 7 days with leukapheresis on days 5, 6, and 7 was found to be safe and effective [see Clinical Studies (14.4)].

In the revised version for the biosimilar, the name "Zarxio" is juxtaposed with "filgrastim" in the very same sentence. This could easily mislead prescribers into thinking that Zarxio either is filgrastim or can be substituted for it interchangeably, neither of which is true. Moreover, the labeling statement misleadingly implies that Zarxio was studied in patients undergoing this particular treatment, but that optimal treatment duration was not established. That is not true—there are no Zarxio data regarding patients undergoing autologous peripheral blood progenitor cell collection and therapy.

A "same labeling" approach also distorts the presentation of risk information for biosimilars, including information about immunogenicity and other potential adverse reactions. Sandoz developed a significant amount of adverse reaction data through its clinical studies that directly compared the frequency of adverse reactions observed in patients using Zarxio and patients receiving Neupogen.[93] None of this information was included in the labeling for Zarxio, which contains only adverse reaction data from clinical trials on Neupogen.[94]

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[92] See 21 C.F.R. § 201.57(c)(15) (labeling ordinarily must "describe the studies that support effectiveness for the labeled indications"); see also FDA, Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, 5-6 (Jan. 2006), http://1.usa.gov/1A3fwAC ("If effectiveness can be determined only by comparison to an active control (superiority or non-inferiority trial) and the identity of the active comparator is important to a clinician's understanding of the drug's effects, the active control data and identity of the comparator should be included in labeling.").

[93] Sandoz Brief at 82-90.

[94] See Zarxio Package Insert, Table 2 (Mar. 2015). http://1.usa.gov/1Ip4O8t.

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Another potential distortion pertains to immunogenicity. The labeling for Neupogen reports that antibodies binding to Neupogen were detected in 3% of patients.[95] The labeling for Neupogen also warns that the "detection of antibody formation" is difficult and therefore warns that the results for Neupogen should not be compared "to other products."[96] A prescriber reading that warning could conclude—rightly—that those results should not be compared to results from studies with other products, including other G-CSF products like lenograstim. The labeling for Zarxio, however, sends a very different message. Sandoz observed zero cases of antibodies binding to Zarxio.[97] Yet the Zarxio labeling does not disclose that result; instead, the labeling for Zarxio copies the 3% incidence of bound antibodies from the Neupogen labeling. The Zarxio labeling also warns that the 3% result should not be compared to results reported for "other filgrastim products."[98] A prescriber reading that warning could conclude—wrongly—that the reported results pertained only to Zarxio, and should not be compared to results from studies with Neupogen. In fact, the exact opposite is true.

In the past, FDA has avoided these types of problems by ensuring that labeling identifies the source of the data included. Prior to the BPCIA, FDA had approved follow-on versions of a few complex products, most notably Omnitrope® (somatropin [rDNA origin] injection), under section 505(b)(2) of the FDCA.[99] To do so, FDA construed 505(b)(2) to allow approval based on a showing that the proposed drug was "highly similar" to a listed drug based on "comparative physicochemical tests, bioassay, preclinical data, pharmacokinetic data, pharmacodynamic data, [and] clinical data" and notwithstanding "any information regarding differences between the proposed drug and the listed drug."[100] According to FDA, this showing of a high degree of similarity made it "scientifically appropriate for the Agency to rely on its finding of safety and effectiveness for the listed drug."[101] FDA's interpretation of section 505(b)(2) is thus directly analogous to the biosimilar approval pathway under the BPCIA.

Nevertheless, FDA cautioned that "a finding of similarity in the context of a 505(b)(2) application does not imply a finding of sameness as that term is used in section 505(j)."[102] Further, as discussed above,[103] the 505(b)(2) pathway does not include a same labeling requirement. Unsurprisingly, the labeling for Omnitrope differs a great deal from the labeling of the RLD somatropin product. Relevant here, the sponsor of Omnitrope—which also happens to have been Sandoz—demonstrated that Omnitrope is highly similar to its RLD by conducting "three sequential, multicenter, phase 3 pivotal trials in pediatric patients with GHD over a 15-month period in which it demonstrated the clinical

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[95] Neupogen Package Insert § 6.2 (Mar. 2015), http://bit.ly/1s2wMyt.

[96] Id.

[97] Sandoz, Advisory Committee Slides, 30 (Jan. 7, 2015), http://1.usa.gov/1Pmotf6.

[98] Zarxio Package Insert § 6.5.

[99] See, e.g., Second Woodcock Statement.

[100] FDA, Citizen Petition Resp., Docket Nos. 2003P-0176, 2004P-0171, 2004P-0231, 2004N-0355, 9 n.23 (May 30, 2006) (Omnitrope Response)

[101] Id.

[102] Id. (emphasis in the original).

[103] Supra n.25-26 & accompanying text.

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comparability of [Omnitrope] and [the RLD] in head-to-head trials."[104] Section 6.2 of the current Omnitrope package insert includes the results from those trials.[105] It also reflects safety results from studies using the RLD, such as "studies in pediatric patients with Prader-Willi Syndrome carried out with another somatropin product."[106] Indeed, the Omnitrope labeling refers to data derived from studies of "another somatropin product" at least 36 times.

In short, when it approved Omnitrope, FDA did not impose a "same labeling" requirement and took steps to ensure that the labeling would carefully distinguish those data that pertained to Omnitrope from those data that pertained to the RLD. This was appropriate because FDA approved Omnitrope based on a showing of a high degree of similarity, not sameness. Zarxio also was found highly similar to, and not the same as, Neupogen based on, among other things, comparative clinical trials. Yet the labeling for Zarxio does not disclose the results of those trials or distinguish data that pertains to the reference product. There is no justification for the radically different approach to the labeling for Zarxio.[107]

C. FDA Violated The APA When It Abandoned The Draft Scientific Guidance's Approach To Biosimilar Labeling.

Serious administrative law questions are raised by FDA's actions in (1) proposing in February 2012 that biosimilar labeling should include clear statements regarding the product, (2) appearing to stand by that proposal for nearly three years of public comment and discussion, (3) approving Zarxio without any such labeling statements in March 2015, and (4) issuing final guidance in April 2015 that omitted the draft guidance's language without any explanation. In these circumstances, FDA's abrupt and unexplained about-face regarding biosimilar labeling violated the APA.

As noted previously in this Petition, FDA's initial guidance under the BPCIA recognized that labeling should play an important role in differentiating biosimilars from reference products. To that end, the draft guidance recommended that biosimilar labeling include "a clear statement" advising that a product was a biosimilar and disclosing whether it was interchangeable with its reference product. The draft guidance recognized that information as "necessary for a health professional to make prescribing decisions."[108] At the time, FDA officials stated that the draft guidance reflected "public input" and addressed the "highest priority issues" that FDA had identified regarding biosimilars.[109] In 2013, an FDA official indicated that FDA still intended for biosimilar labeling to contain "differences"

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[104] Omnitrope Response at 10.

[105] See Omnitrope Package Insert, § 6.2, Tables 1 and 2 (August 2014), http://1.usa.gov/1EVx2W6

[106] Id. § 6.2.

[107] Notably, Health Canada requires the labeling for the biosimilar to provide the key data "on which the decision for market authorization was made." Canada Biosimilar Guidance § 2.5. FDA should adopt similar requirements for biosimilars marketed here in the United States.

[108] Draft Scientific Guidance at 21 (emphasis added).

[109] FDA, Biosimilar Biological Products – Biosimilar Guidance Webinar, 12 (Feb. 15, 2012), http://1.usa.gov/1L4SY3a.

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from reference product labeling "to distinguish" the biosimilar from the reference product.[110] In 2014, the same official stated that, in the Agency's view, the 2012 draft guidance had been "well received."[111]

Nevertheless, when the final version of the guidance was issued in April 2015, it contained no discussion of biosimilar labeling—the entire labeling discussion was omitted.[112] The Federal Register notice announcing the final guidance did not acknowledge, much less explain, this significant change. The notice stated that the Draft Scientific Guidance had been revised in only four ways: (1) to provide "further clarification" regarding the comparative studies needed to establish biosimilarity; (2) to provide "additional information" regarding clinical trial design; (3) to explain "when a comparative clinical trial may not be needed"; and (4) to make certain "editorial changes . . . to improve clarity."[113]

FDA's reversal is especially surprising given the broad support for the draft guidance's approach to biosimilar labeling. At a public hearing in 2010, diverse stakeholders emphasized the need for biosimilar labeling to include information necessary to enable appropriate prescribing. Speakers representing affected patient populations and physician groups urged FDA to require clear labeling statements,[114] including "accurate, specific, and comprehensive information about the actual product, not the reference product."[115] Representatives of the innovator industry also urged FDA to require biosimilar labeling to "clearly state that it is a biosimilar"[116] and "to include a prominent statement regarding its . . . interchangeability."[117] Others did as well.[118] To our knowledge, no speaker expressed a contrary view.

After the hearing, written comments submitted to FDA also supported including this information in biosimilar labeling. The International Society for Pharmacoepidemiology stated that it "is of overriding importance" that "health care professionals should be fully informed as to the precise product administered [and] its relationship to the reference product."[119] The National Psoriasis

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[110] Jeff Overly, Biosimilars Guidance, Drugmaker Grades Coming, FDA Says, Law360 (Oct. 2, 2013), http://bit.ly/1bVbsqr.

[111] FDA, Update on the Development and Approval of Biosimilar Products: Where are we now and where are we headed?, 9 (May 14, 2014), http://1.usa.gov/1ymkMKd.

[112] See Final Scientific Guidance at 22.

[113] 80 Fed. Reg. 24258, 24529 (Apr. 30, 2015).

[114] Tr. of Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products, 27 (Nov. 2, 2010) (statement of Dr. Janet Wyatt, Arthritis Foundation).

[115] Id. at 205 (statement of Dr. Gregory Schimizzi, Coalition of State Rheumatology Organizations).

[116] Id. at 219-20 (statement of Jim Shehan, Novo Nordisk, Inc.).

[117] Id. at 234 (statement of Dr. F. Owen Fields, Pfizer, Inc.); accord Tr. of Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products, 206, 325, 343 (Nov. 3, 2010) (statements of Dr. Joseph P. Miletich, Amgen, Inc., Marie Vodicka, PhRMA, and Sara Radcliffe, BIO, respectively).

[118] See Tr. of Part 15 Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products, 254-55 (Nov. 3, 2010) (statement of Dr. Judy Ruckman, CBR Int'l Corp.).

[119] Int'l Soc. for Pharmacoepidemiology, Comments to Docket No. FDA-2010-N-0477, 5 (Dec. 23, 2010).

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Foundation stated that "[c]lear and specific labeling . . . to distinguish between reference products and biosimilars is of utmost importance."[120] The innovative industry likewise stated that FDA should require "the labeling of every biosimilar that does not meet the interchangeability standard to include a statement that the product is not interchangeable."[121] A leading biosimilar developer also recommended that biosimilars not determined to be interchangeable "should have a standard statement on the label noting that they are a biosimilar and not interchangeable with the brand product."[122] At least two other biosimilar developers concurred.[123] In short, there was broad agreement that biosimilar labeling must contain clear statement regarding product status.

Public support for FDA's original proposal continued after the 2012 guidance was issued. In written comments, the Alliance for Safe Biologic Medicines agreed that biosimilar labeling should disclose the product's "[s]tatus as non-interchangeable or interchangeable."[124] The American Association of Clinical Endocrinologists stated that labeling should "clearly identify the product as a biosimilar, and should indicate whether the product has or has not been determined to be interchangeable with the reference product."[125] Similar comments were submitted by the Colon Cancer Alliance, the National Kidney Foundation, and the Global Healthy Living Foundation.[126] The innovative

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[120] Nat'l Psoriasis Found., Comments to Docket No. FDA-2010-N-0477, 5 (Dec. 30, 2010); accord Nat'l Kidney Found., Comments to Docket No. FDA-2010-N-0477, 2 (Dec. 22, 2010); Ovarian Cancer Nat'l Alliance, Comments to Docket No. FDA-2010-N-0477, 2; Am. Acad. of Dermatology Ass'n, Comments to Docket No. FDA-2010-N-0477, 2 (Dec. 31, 2010).

[121] Johnson & Johnson, Comments to Docket No. FDA-2010-N-0477, 7 (Dec. 23, 2010); accord Merck & Co., Inc., Comments to Docket No. FDA-2010-N-0477, 3, 5 (Dec. 23, 2010); Amgen Inc., Comments to Docket No. FDA-2010-N-0477, 6, 50-51, 53, 67 (Dec. 29, 2010); BioGen Idec, Comments to Docket No. FDA-2010-N-0477, 6 (Dec. 29, 2010); Genentech, Inc., Comments to Docket No. FDA-2010-N-0477, 5 (Dec. 17, 2010); PhRMA, Comments to Docket No. FDA-2010-N-0477, 2, 14-16, (Dec. 23, 2010); BIO, Comments to Docket No. FDA-2010-N-0477, 2, 18-19, 27-28 (Dec. 23, 2010).

[122] Momenta Pharm., Inc., Comments to Docket No. FDA-2010-N-0477, 7 (Dec. 22, 2010).

[123] Teva Pharm. Indus., Inc., Comments to No. Docket FDA-2010-N-0477, 3 (Dec. 28, 2010) ("Teva also recommends that FDA use product labeling as a key communication tool. For example, as part of the "Description" section of the product labeling, FDA can clearly identify and state that the product is biosimilar and interchangeable." (emphasis removed)); Pfizer Inc., Comments to Docket No. FDA-2010-N-0477, Appx. (Dec. 22, 2010) ("The label would include a prominent statement regarding its biosimilarity and/or interchangeability status with regard to each indication.").

[124] Alliance for Safe Biologic Medicines, Comments to No. Docket FDA-2011-D-0605, 4 (Apr. 16, 2012).

[125] Am. Ass'n of Clinical Endocrinologists, Comments to Docket No. FDA-2011-D-0605, 2 (Apr. 16, 2012).

[126] Colon Cancer Alliance, Comments to Docket No. FDA-2011-D-0605, 2 (Mar. 22, 2012) ("Physicians should know if they are prescribing a biologic or a biosimilar . . . ."); Nat'l Kidney Found., Comments to Docket No. FDA-2011-D-0605, 4 (Apr. 12, 2012) ("the package insert for a biosimilar should provide testing information, including the number of studies, the study circumstances, the number of study participants, and the duration of study, both for the referenced product, as well as data provided for the purpose of establishing equivalence"); Global Healthy Living Found., Comments to Docket No. FDA-2011-D-0605, 4 (Apr. 4, 2012) (advocating a "unique and distinctive . . . labeling system").

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industry also was unanimously in support of the original proposal.[127] Many lengthy comments submitted by generic manufacturers did not object.[128] In fact, some comments from the generic industry supported the need for complete labeling information. For instance, the Novartis Group (which includes Sandoz) endorsed FDA's WHO policy paper from September 2006 as the proper approach to postmarket safety monitoring of biosimilar products.[129] The Generic Pharmaceutical Association did the same.[130] That policy paper stated that one of the most important mechanisms to guard against improper substitution of non-interchangeable drugs is "specific labeling" regarding interchangeability.[131]

After the Draft Scientific Guidance was issued, the Agency convened a second public hearing. Once again, numerous and diverse stakeholders spoke in support of the labeling recommendations in the Draft Scientific Guidance.[132] Written submissions were likewise supportive.[133] Through all of this public participation, there was little opposition to the labeling recommendations in the draft.

In fact, we have identified only one substantive challenge to those labeling proposals. In April 2012, Mylan Inc. (Mylan) argued that the labeling proposals in the Draft Scientific Guidance were "unprecedented"[134] and would conflict with BPCIA because that statute "requires that biogeneric labeling must be the same as that of the reference product except for statutorily-permissible differences."[135] Mylan is, quite simply, incorrect. As discussed above (§ III.A), the BPCIA does not contain a same labeling requirement. Such a requirement exists for generic drugs because it is explicit in sections 505(j)(2)(v) and 505(j)(4)(G). In contrast, the three provisions of the BPCIA that were cited by Mylan respectively state that biosimilars must be "highly similar" to their reference products, must seek approval for conditions of use that were "previously approved for the reference product," and must

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[127] BIO, Comments to Docket No. FDA-2011-D-0605, 12 (Apr. 16, 2012); PhRMA, Comments to Docket No. FDA-2011-D-0605, 18-19 (Apr. 16, 2012); see also, e.g., Allergan Inc., Comments to Docket No. FDA-2011-D-0605, 7 (Apr. 16, 2012); Amgen Inc., Comments to Docket No. FDA-2011-D-0605, 28 (Apr. 16, 2012); Bayer Healthcare LLC, Comments to Docket No. FDA-2011-D-0605, 4-5 (Apr. 16, 2012); Biogen Idec, Comments to Docket No. FDA-2011-D-0605, 12 (Apr. 16, 2012); EMD Serono, Comments to Docket No. FDA-2011-D-0605, 9-10 (Apr. 15, 2012).

[128] See, e.g., Momenta Pharm., Inc., Comments to Docket No. FDA-2010-N-0605 (Apr. 13, 2012) (no discussion of labeling requirement in eight pages of written comments); Teva Pharm. Indus., Inc., Comments to Docket No. FDA-2010-N-0605 (Apr. 23, 2012) (no discussion of labeling requirements in ten pages); Watson Pharm., Inc., Comments to Docket No. FDA-2010-N-0605 (Apr. 16, 2012) (no discussion of labeling requirement in twelve pages).

[129] Novartis, Comments to Docket No. FDA-2010-N-0605, 30 & n.57 (Apr. 13, 2012).

[130] Generic Pharm. Ass'n, Comments to Docket No. FDA-2010-N-0605, 23. (Apr. 16, 2012).

[131] WHO Policy Paper.

[132] See Tr. of Part 15 Public Hearing, 132 (May 11, 2012) (statement of Dr. Marcie Bough, American Pharmacist Association); id. at 186-87 (statement of Dr. Joseph P. Miletich, Amgen, Inc.); id. at 194 (statement of Dr. Michelle Rohrer, Genentech); id. at 280 (statement of F. Owen Fields, Pfizer, Inc.); id. at 350 (statement of Sara Radcliffe, BIO).

[133] See, e.g., Questcor Pharm., Inc., Comments to Docket No. FDA-2011-D-0618, 5 (May 25, 2012).

[134] Mylan, Inc., Comments to Docket No. FDA-2010-N-0605, 4, 22-23 (Apr. 16, 2012).

[135] Id. at 22.

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have the same dosage form, strength, and route of administration as the reference product.[136] None of those provisions imposes a "sameness" standard on biosimilar labeling.

Given this record, FDA's decision to reverse course and adopt a same labeling approach for biosimilars is arbitrary and capricious. As the United States Supreme Court recently reiterated, an agency's interpretations of the law remain subject to the constraints imposed by the APA.[137] At a minimum, the APA imposes an "unwavering" obligation on agencies to provide a reasoned explanation for their policies.[138] In the circumstances presented here—where FDA initially stated that clear statements were "necessary" for safe prescribing; where there was broad agreement as to the importance of these labeling statements to patient care; and where FDA is implementing an entirely new biosimilar approval pathway—FDA's silent abandonment of the labeling recommendations in the Draft Scientific Guidance was improper. FDA cannot abandon that proposal without comment, leaving regulated entities and other key stakeholders to guess its "unspoken thoughts."[139]

IV. OTHER REQUIRED INFORMATION

A. Environmental Impact

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

B. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

C. Certification

I certify that, to my best knowledge and belief: (a) this Petition includes all information and views upon which the Petition relies; (b) this Petition includes representative data and/or information known to the petitioner which are unfavorable to the Petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the Petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this Petition is submitted on or about the following date: March 6, April 24, and April 28, 2015. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or

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[136] 42 U.S.C. § 262(i)(2)(A), 262(k)(2)(a)(iii), 262(k)(2)(A)(iv).

[137] Perez v. Mortgage Bankers Ass'n, 135 S. Ct. 1199, 1209 (2015) (citing FCC v. Fox Television Stations, Inc., 556 U.S. 502, 515 (2009)).

[138] Judulang v. Holder, 132 S. Ct. 476, 479 (2011).

[139] CSX Transp., Inc. v. Surface Transp. Bd., 584 F.3d 1076, 1080 (D.C. Cir. 2009); see id. at 1081 ("[O]ur cases finding that a rule was not a logical outgrowth have often involved situations where the proposed rule gave no indication that the agency was considering a different approach, and the final rule revealed that the agency had completely changed its position").

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expect to receive those payments from the following persons or organizations: AbbVie, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this Petition.

Respectfully Submitted,

Perry C Siatis/cb

Perry C. Siatis
Vice President
Biotherapeutics and Legal

Neal Parker

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