abbvie

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January 16, 2018

Centers for Medicare & Medicaid Services,
Department of Health and Human Services
7500 Security Boulevard
Attention: CMS–4182–P
Baltimore, MD 21244

RE: Contract Year 2019 Policy and Technical Changes to the Medicare Advantage, Medicare Cost Plan, Medicare Fee-for-Service, the Medicare Prescription Drug Benefit Programs, and the PACE Program, Proposed Rule (CMS-4182-P)

Dear Administrator Verma:

AbbVie appreciates the opportunity to comment on the Centers for Medicare & Medicaid Services's (CMS's or the agency's) Contract Year (CY) 2019 Policy and Technical Changes to the Medicare Advantage, Medicare Prescription Drug Benefit Programs Proposed Rule (the proposed rule).[1] At AbbVie, we strive to make a remarkable impact in the lives of patients. We are a global, research-based biopharmaceutical company with 29,000 people who are dedicated to developing and delivering a consistent stream of innovative new medicines with distinct and compelling patient benefits. With leading scientific and industry capabilities, a comprehensive approach to tackling the toughest health care challenges and a track record of achievement, we are a long-term partner in the pursuit of better health outcomes. Consistent with that mission, we are also committed to sustaining the success of the Medicare Part D Prescription Drug Benefit Program.

AbbVie commends the efforts of CMS to implement changes to the Medicare Advantage (MA, Part C) and Prescription Drug Benefit (Part D) programs to improve program quality, accessibility and affordability for beneficiaries. We are concerned, however, with CMS's proposed treatment of biosimilar products as generic drugs for purposes of non-low income subsidy catastrophic and low-income subsidy (LIS) cost sharing.

Since the Medicare Part D Prescription Drug Benefit was first implemented in a final rule published in 2005, "generic drug" has been defined at 42 C.F.R. § 423.4 as "a drug for which an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [FDCA] (21 U.S.C. 355(j)) is approved."[2] In this year's proposed rule, CMS proposes to add biosimilars to the definition of "generic drug" for purposes of non-LIS catastrophic and LIS cost sharing only. For the reasons discussed below, we believe that changing the definition of generic drug for these purposes is not legally supportable and would not be good public policy. Notably, CMS proposes *not* to treat biosimilars as generic drugs for purposes of transition or midyear formulary

[1] CMS, Medicare Program; Contract Year 2019 Policy and Technical Changes to the Medicare Advantage, Medicare Cost Plan, Medicare Fee-for-Service, the Medicare Prescription Drug Benefit Programs, and the PACE Program, Proposed Rule, 82 Fed. Reg. 56,336 (Nov. 28, 2017).
[2] *See* 70 Fed. Reg. 4,194, 4,527 (Jan. 28, 2005).

changes. We support this position and believe it underscores the point that biosimilars are *not* generic drugs and therefore should *not* be treated as such. We discuss each of these topics in more detail below.

Treatment of Follow-On Biological Products as Generics for Non-LIS Catastrophic and LIS Cost-Sharing

I. It is well accepted that biosimilars and generics are fundamentally different.

Biological (protein) products licensed under the PHSA are fundamentally different–as a scientific matter–from small-molecule drugs approved under the FDCA. Most small-molecule drugs are chemically synthesized, simple, stable, homogenous, easily characterized, and easily replicable. Biological products, by contrast, are generally manufactured in living systems, significantly larger and more complex, difficult or sometimes impossible to characterize, often heterogeneous, and highly sensitive to changes in raw materials and manufacturing conditions.[3] As senior FDA officials have explained, "[p]rotein products are typically much larger, more complex molecules than non-protein, small molecule drugs."[4] Moreover, they "generally cannot be fully characterized using available analytical techniques."[5] Further, "protein products are often heterogeneous mixtures of molecules that vary slightly in molecular structure."[6] And, in contrast to small-molecule drugs, "proteins fold upon themselves and form specific conformations that can be critical to biological activity."[7] Even "well-characterized, highly purified proteins exhibit micro-heterogeneity (that is, slight differences in structure between essentially identical molecules, such as in the saccharide portion of a glycoprotein)."[8] Also, biotechnology-derived products can "vary slightly from lot to lot even when the same manufacturing process is used."[9] Finally, the "quality and nature of natural-source products can also vary depending on factors such as variability of the source material (for example, time of year of harvest, species) and the processes used to extract and purify the product."[10]

Given the structural complexity of biological products, a biosimilar sponsor would not be able to demonstrate that its product has the same active ingredient as the reference product, as would be required for approval of a generic small-molecule drug product.[11] For a small-molecule drug, the FDA officials explained that "the molecular structure of such a drug can usually be verified

[3] A handful of drugs approved under the FDCA are naturally-derived or recombinant protein products, meet the statutory definition of "biological product" as amended in the Biologics Price Competition and Innovation Act (BPCIA), and will be deemed licensed under the PHSA in 2020. *See* Patient Protection and Affordable Care Act (ACA), Pub. L. No. 111-148, § 7002(e)(4), 124 Stat. 119, 817 (2010). As used in this document, "small-molecule drugs" refers not to those products, but instead to the vast majority of drugs that are the subject of approved new drug applications (NDAs) or abbreviated new drug applications (ANDAs) and are simple, easy to characterize, and chemically synthesized.

[4] Janet Woodcock, et al., "The FDA's assessment of follow-on protein products: A historical perspective," 6 *Nature Rev. Drug Discov. 437, 438* (2007). This article, published in April 2007, appeared following hearings in March 2007 in both the House and Senate. An additional House hearing followed in May 2007.

[5] Woodcock, supra note 4 at 438.

[6] *Id*.

[7] *Id*.

[8] *Id*.

[9] *Id*.

[10] *Id*.

[11] 21 U.S.C. § 355(j)(2)(A)(ii).

analytically," and consequently, "it is fairly easy for a generic-drug manufacturer to produce a duplicate product containing an active ingredient that is the same as the active ingredient in an innovator's approved drug product."[12] By contrast, as the current Director of FDA's Center for Drug Evaluation and Research (CDER), Dr. Janet Woodcock, testified repeatedly during the legislative process that led to the Biologics Price Competition and Innovation Act (BPCIA), "the idea of sameness. . . will not usually be appropriate for more structurally complex molecules of the type generally licensed as biological products."[13] Dr. Woodcock further explained: "Unlike small molecule drugs whose chemical composition can easily be determined to be the same as an approved product, the very nature of protein products makes comparisons of one protein to another, including comparisons to establish safety and efficacy, more scientifically challenging."[14] For this reason, "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."[15]

Therefore, biosimilar applicants must demonstrate (among other requirements) that the proposed follow-on product is "biosimilar" to the reference product—meaning that it is "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency."[16] The fact that the active components of biosimilar and reference products are similar, but not the same, means that they may not be presumed to behave in identical ways in each condition of use approved for the reference product, particularly at the individual patient level. [17]

The different review standard for biosimilars is also attributed to concerns related to immunogenicity. Unlike small-molecule drugs, the human immune system may identify and respond to biologics as the body produces antibodies in an attempt to protect itself. In some cases, this response—known as immunogenicity—can lead to a lack of effectiveness, including for patients who previously had been doing well on the biologic.[18] Immunogenicity can also result in side effects, some of them serious.[19] As FDA has noted, the "safety consequences of

[12] Woodcock, *supra* note 4, at 437.
[13] *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight & Government Reform*, 110th Cong. at 23 (2007) (prepared statement of Janet Woodcock, M.D., Deputy Comm'r, Chief Medical Officer, FDA); *see also Follow-on Protein Products*, Statement of Janet Woodcock, M.D., before the H. Comm. on Oversight and Gov't Reform (Mar. 26, 2007) (First Woodcock Statement); *Assessing the Impact of a Safe and Equitable Biosimilar Policy*, Statement of Janet Woodcock, M.D., before the Subcomm. on Health, H. Comm. On Energy and Commerce (May 2, 2007) (Second Woodcock Statement).
[14] Second Woodcock Statement, *supra* note 13, at 28.
[15] *Id*. at 30. *See also* FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Apr. 2015) (FDA Scientific Considerations Guidance), at 5 ("Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product.").
[16] 42 U.S.C. § 262(i)(2).
[17] A biosimilar may be approved for fewer than all of the reference product's approved conditions of use. FDA, *Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at 7-8 (Apr. 2015).
[18] *See generally* FDA, Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products (Aug. 2014) (FDA Immunogenicity Guidance)
[19] *Id*. at 3.

immunogenicity may vary wildly and are often unpredictable in patients administered therapeutic protein products."[20]

Immunogenicity can result from product-specific factors, patient-specific factors, or treatment-specific factors, such as switching between biologic therapies. Product-specific factors—such as product aggregates, impurities with adjuvant activity, formulation components, and container closure systems—can increase or decrease the risk of immunogenicity,[21] which is why each biologics license application, including a biosimilar application, generally must include a robust clinical assessment of immunogenicity.[22] Patient-specific factors also can increase or decrease the risk of immunogenicity. These patient-specific factors include concomitant medications, general immunologic status, age, prior exposure to the protein or structurally similar proteins, and genetic factors.[23] This means, in essence, that immunogenicity can vary from patient to patient, population to population, and indication to indication.[24]

Treatment-specific factors, such as switching or alternating between biological therapies may induce or strengthen an immunogenicity reaction, [25] even when that switch is between highly similar, that is biosimilar, biologic therapies.[26] The full impact of switching or alternating between a reference product and a biosimilar is unknown and in our view the data available today regarding currently-marketed biosimilars and their reference products have limitations[27] and are inconclusive regarding the impact of switching on efficacy, safety, and immunogenicity.[28] Nevertheless, to account for the possibility that an immunogenicity reaction

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[20] *Id*.

[21] *Id*. at 12-21.

[22] *See generally id*. FDA has explained that a biosimilar applicant should assess "the nature of the immune response (e.g., anaphylaxis, neutralizing antibody), the clinical relevance and severity of consequences (e.g., loss of efficacy of life-saving therapeutic and other adverse effects), the incidence of immune responses, and the population being studied." FDA Scientific Considerations Guidance, at 16-18.

[23] FDA Immunogenicity Guidance, at 9-12.

[24] *See id*. For instance, the rate of immunogenicity associated with infliximab is said to range from 7% to 61% across indications. *See* Bradley J. Scott, et al., *Biosimilar monoclonal antibodies: A Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation*, J. Clin. Pharmacol. S123-S127 5 (2015).

[25] *See*, *e.g*., Gert Van Assche *et al*., *Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: Prospective randomised SWITCH trial*, 61 Gut. 229 (2012).

[26] *Biosimilar Implementation: A Progress Report from FDA, Hearing Before the Subcomm. on Primary Health & Retirement Security of the S. Comm. on Health, Education, Labor & Pensions*, 114th Cong. 11 (2015) (statement of Janet Woodcock, M.D., Director, Center for Drug Evaluation & Research, FDA)33-34 ("[W]hat the concern has been is that this continued switching could raise that immunity – sort of provide a booster effect and cause [untoward] effects."). *See also Freddy* Faccin et al. *The design of clinical trials to support the switching and alternation of biosimilars'.* Expert Opin Biol Ther. 1445–53, 1450 (2016) ("A sudden change in molecular motifs presented to the immune system can trigger an immune response and such antigenic discontinuity may arise when switching or alternating between originator and biosimilar therapies. Further, repeatedly presenting different sets of epitopes (as could be the case for an originator and its biosimilar) may produce a synergistic boost of immune response primed by the initial therapy switch; the timing between these switches could also critically affect the magnitude of the response").

[27] *See* Faccin et al. *, supra, 1446-50, 1451 ("*Suboptimal design of existing biosimilar switching trials limits the amount and potentially the quality and interpretation of data. Therefore, these trials fall short of fully addressing clinically valid questions and concerns regarding the practice of changing therapy to a drug that is not expected to improve clinical outcome in a patient who is responding to their current therapy.").

[28] See commentary from Roy Fleischman, *Biosimilars in rheumatology—Why, how and when in 2017*, Nat. Rev. Rheumatol. 701, 702-703 (2017) ("This finding raises the possibility that in the 'real world', even a single switch is

might result from substitution of a biosimilar product for the reference product, Congress provided for an interchangeability designation—distinct from biosimilarity—such that a biosimilar "may be substituted for the reference product without the intervention of" the prescriber if, among other considerations, "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[29] Clinical data evaluating the effect of an alternation or switch generally are required to meet this standard.[30] To date, FDA has not approved any biosimilar to be interchangeable with its reference product.

II. Expanding the definition of "generic drug" to include biosimilars is not legally supportable.

As a legal matter, adding biosimilars to the definition of "generic drug" for the purpose of Part D cost-sharing would not be consistent with Congress's intent or with fundamental principles of statutory construction. First, there is ample evidence that Congress distinguishes between generic drugs and biosimilars and does not use the term "generic drug" to encompass biosimilars. Second, assigning that term a different meaning only for purposes of certain cost-sharing provisions would be contrary to the core principle of statutory interpretation that a term is presumed to mean the same thing when it is used multiple times in the same or related legislation.

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not efficacious in a reasonable number of patients . . . . The recommendations proposed by Kay and colleagues could indeed be correct, but cannot be confirmed by the evidence they cite and will require future verification to be fully accepted as valid. A key question with respect to the utility of biosimilars is whether repetitive switching between a bio-originator and a biosimilar, as well as between multiple biosimilars, is safe and effective.. . . . . No trials have yet addressed this strategy, so until researchers have confirmed this assumption, physicians and patients should remain cautious about multiple switches between biosimilars.") and commentary from Fabrizio Cantini & Maurizio Benucci, *Switching from the bio-originators to biosimilar: Is it premature to recommend this procedure?*, Ann. Rheum. Dis. 10.1136/annrheumdis-2017-212820 (published online ahead of print Dec. 29, 2017) ("However, we have some concerns regarding recommendation 6 on the efficacy and safety of switching from the originator biologic to the respective biosimilar. . . . [S]uch recommendation seems not sufficiently supported by the evidence because available data do not allow to draw definitive conclusion on the switching strategy. . . . . To conclude, in our opinion, available data from real-world clinical practice, somewhat conflicting with those of RCTs, seem to suggest that it is premature to formulate recommendations on the switching strategy from the bio-originator to its biosimilar."). Both comments disagree with the reported expert consensus recommendations in Jonathan Kay et al., *Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases*, 77 Ann. Rheum. Dis. 165–174, 172 (2017) ("The group believed that adequate evidence exists to support the decision to switch from a biologic, which no longer is protected by patent, to its biosimilar. . . . However, there remained concern about switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions because adequate studies have not yet been conducted to assess these circumstances."). *See also* Robert Moots et al., *Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: Considerations for the clinician*, 19 Curr. Rheum. Rep. 37, 46 (2017) (meta-analysis of switching data for currently marketed biosimilars, concluding that "[t]he safety of switching to these biosimilars has not yet been fully demonstrated in terms of their long-term efficacy, safety, and immunogenicity. Thus, data from pharmacovigilance programs are needed in order to adequately inform clinical decision-making in relation to switching between these compounds.")

[29] 42 U.S.C. § 262(k)(4). This particular provision applies only for those products that might be used by a patient more than once.

[30] *See* FDA Interchangeability Draft Guidance, at 4. .

A. Congress has consistently interpreted "generic drug" to exclude biosimilars.

The terms "generic drug" and "biosimilar" are terms of art that have well-understood meanings within the pharmaceutical industry, reflecting the significant scientific and statutory distinctions between the two terms. "Generic drug" has always been understood to mean a follow-on small-molecule medicine that is therapeutically and pharmaceutically equivalent to the reference drug that it copies, because the two products contain identical amounts of the same active ingredient and that active ingredient has equivalent bioavailability in the patient. Indeed, the Supreme Court has described the term "generic drug" to mean "a drug designed to be a copy of a reference listed drug . . . and thus identical in active ingredients, safety, and efficacy."[31]

When Congress enacted Medicare's cost-sharing provisions in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) as part of Medicare Part D, it took into account the traditional, accepted legal meaning of "generic drug."[32] As the Supreme Court has recognized, it is a "'cardinal rule of statutory construction' that 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.'"[33] Accordingly, when Congress enacted the Part D cost-sharing provisions, it understood "generic drug" to mean an equivalent version of a small-molecule drug approved through an Abbreviated New Drug Application (ANDA).[34]

Congress's understanding of "generic drug" did not change when it subsequently created the distinct pathway for the approval of biosimilar products through the BPCIA, which became law in March 2010 as part of the Patient Protection and Affordable Care Act (ACA).[35] The BPCIA described follow-on biological products as "biosimilars" rather than "generic drugs" because Congress understood the important and well-recognized differences between the two. Indeed, when Representative Eshoo introduced her bill proposing to govern biosimilars, Pathway for Biosimilars Act, she discussed those differences at length and emphasized that

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[31] *PLIVA v. Mensing*, 564 U.S. 604, 612 n.2 (2011); *see also United States v. Generix Drug Corp.*, 460 U.S. 453, 454 (1983) ("The term 'generic drug' is used to describe a product that contains the same active ingredients . . . as a so-called 'pioneer drug' that is marketed under a brand name.").

[32] *See* Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 101(a)(2), 117 Stat. 2066, 2077, 2108 (amending Social Security Act (SSA), Pub. L. No. 74-271, 49 Stat. 620 (1935), as amended, at §§ 1860D-2(b)(4), 1860D-14(a)(1)(D)(ii) (codified at 42 U.S.C. §§ 1395w-102(b)(4), 1395w-114(a)(1)(D)(ii))).

[33] *FAA v. Cooper*, 566 U.S. 284, 292 (2012) (quoting *Molzof v. United States*, 502 U.S. 301, 307 (1992)); *see also McDermott Int'l, Inc. v. Wilander*, 498 U.S. 337, 342 (1991) (when a statute uses a term of art, the Court assumes that "Congress intended it to have its established meaning" absent "contrary indication").

[34] Other provisions of the public law that created Part D reinforce this conclusion. The MMA did not define the term "generic drug" for purposes of Part D. It did, however, define that term for purposes of other provisions—in the same public law that created Part D—that required the filing of certain drug-related agreements with the Federal Trade Commission and the Department of Justice. In that context, Congress provided: "The term 'generic drug' means a drug for which an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act is approved." MMA § 1111(6), 117 Stat. at 2461. That definition, although not directly applicable to the Part D copayment provisions, is a "strong contextual clue" as to how Congress understood the term "generic drug" when it enacted Part D. *Taniguchi v. Kan Pacific Saipan, Ltd.*, 566 U.S. 560, 570-72 (2012) (considering other uses of the term "interpreter" in the same public law that enacted the provision at issue).

[35] *See* ACA, Pub. L. No. 111-148, §§ 7001-7003, 2(e)(4), 124 Stat. 119, 804–821 (2010) (codified in relevant part at 42 U.S.C. § 262).

"biosimilars — *unlike generic drugs* — will not be chemically identical to the reference product."[36]

At the time Congress created the biosimilar pathway, it did not express any intent that CMS should now understand the term "generic drug" to include biosimilars. To the contrary: as part of the ACA, Congress amended the Medicare Part B program to specifically address payment for biosimilar products, establishing a unique reimbursement formula for those products.[37] Congress also included the following distinct definition of the term "biosimilar": "a biological product approved under an abbreviated application for a license of a biological product that relies in part on data or information in an application for another biological product licensed under section 351 of the Public Health Service Act."[38] Congress addressed the Medicare reimbursement of biosimilars with respect to Medicare Part B at the time it created the biosimilar approval pathway. It did not do so with respect to Medicare Part D, despite the fact that CMS was operating using a definition of "generic drug" that excluded biosimilars. The amendments to Part B indicate that "Congress knew how to draft the kind of statutory language" that would have expanded existing Medicare provisions to encompass biosimilars; accordingly, Congress's failure to similarly amend Part D gives rise to a strong inference that Congress did not intend for biosimilars to be shoehorned into existing statutory provisions in Part D that refer only to "generic drugs."[39] It is axiomatic that "[w]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."[40]

Legislation enacted since 2010 reflects Congress's continued practice of distinguishing between generic drugs and biosimilars. For example, in 2012, Congress enacted—in separate titles of the same public law — the Generic Drug User Fee Amendments of 2012, which authorized FDA to impose fees relating to "generic drug submissions" made under 21 U.S.C. § 355(j), and the

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[36] 155 Cong. Rec. 7683 (2009) (emphasis added); *see also* H.R. Rep. No. 111-299, at 740–42 (2009) (distinguishing between proposed new biosimilar approval process and preexisting process "for approving generic chemical drugs"); *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Subcomm. on Health*, 110th Cong. 13 (2007) (prepared statement of Rep. Joe Barton) (arguing that describing biosimilars as "generic" is "not accurate and muddies the waters" because "[g]eneric denotes that the products are the same and can be freely substituted").

[37] *See* ACA § 3139, 124 Stat. at 439-40.

[38] *Id.* § 3139(a)(2) (codified at 42 U.S.C. § 1395w-3a(c)(6)(H)). Medicare Part B distinguishes between multiple-source drugs, single-source drugs, biological products, and biosimilar biological products, giving each of these terms different meanings. *Compare* 42 U.S.C. § 1395w-3a(b)(3) (addressing payments for multiple source drugs) with *id.* § 1395w-3a(b)(4) (addressing payments for "single source drug or biological"). A generic drug can qualify either as a multiple-source drug or, when the branded product has left the market, as a single-source drug. In the Medicare Act's cost-sharing provisions, Congress refers to "generic drugs" and "preferred drug[s] that [are] multiple source drug[s]," and has never revised those provisions to address biological products or biosimilars. *See* 42 U.S.C. §§ 1395w-102(b)(4); 1395w-114(a)(1)(D)(ii).

[39] *State Farm Fire & Cas. Co. v. United States ex rel. Rigsby*, 137 S. Ct. 436, 444 (2016) (that Congress mandated dismissal as a remedy for violations of some provisions of False Claims Act shows that Congress did not intend dismissal to be mandatory for violations of other provisions); *see also, e.g., Council for Urological Interests v. Burwell*, 790 F.3d 212, 221 (D.C. Cir. 2015) ("Comparing [two statutory provisions] shows that Congress knew how to permit per-click payments explicitly, suggesting that the omission in this particular context was deliberate.").

[40] *Dean v. United States*, 556 U.S. 568, 573 (2009) (quoting *Russello v. United States*, 464 U.S. 16, 23 (1983)); *see also, e.g., Mississippi ex rel. Hood v. AU Optronics Corp.*, 134 S. Ct. 736, 742 (2014); *Jawad v. Gates*, 832 F.3d 364, 370 (D.C. Cir. 2016).

Biosimilar User Fee Act of 2012, which authorized FDA to impose fees relating to "biosimilar biological product applications" submitted under 42 U.S.C. § 262(k).[41] Those provisions were separately reauthorized in the FDA Reauthorization Act of 2017 (FDARA), which also includes a title called "Improving Generic Drug Access" that defines "generic drug" as one approved under 21 U.S.C. § 355(j) (and therefore excludes biosimilars).[42] Indeed, as far as AbbVie is aware, where Congress has adopted a statutory definition of "generic drug," both before and after the creation of the biosimilar pathway, it has defined that term in a way that excludes biosimilars. By contrast, when Congress means to refer to both generic drugs and biosimilars, it uses both terms.[43]

Because Congress consistently has drawn a clear distinction between generic drugs and biosimilars, CMS's proposed interpretation of "generic drug" to include biosimilars cannot reasonably be claimed to reflect legislative intent.

B. CMS cannot assign "generic drug" a unique meaning only for purposes of the two cost-sharing provisions.

CMS acknowledges that the term "generic drug" appears in "many places in the Part D statute."[44] Yet CMS does not propose to define "generic drug" to include biosimilars everywhere it appears in the statute.[45] Instead—because treating biosimilars as generic drugs elsewhere in Part D also would create significant problems[46]—CMS proposes to assign "generic drug" different meanings for different provisions in the same statute. But CMS's proposed approach would violate the cardinal principle of statutory construction that "identical words used in different parts of the same act are intended to have the same meaning."[47]

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[41] *See* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, tit. III–IV, 126 Stat. 993, 1008–39 (2012) (codified in relevant part as amended at 21 U.S.C. §§ 379j-41 to -43 and §§ 379j-51 to -53).
[42] *See* FDARA, Pub. L. No. 115-52, tit. III–IV, 131 Stat. 1005, 1020–35 (2017) (reauthorizing both user fee programs through the Generic Drug User Fee Amendments of 2017 and the Biosimilar User Fee Amendments of 2017); *id.* tit. VIII, § 803, 809(c)(2), 131 Stat. at 1070, 1075 (codified in part at 21 U.S.C. § 356h(e)(1)).
[43] *See, e.g.*, *id.* § 609, 131 Stat. at 1051 (encouraging the HHS Secretary to "commit to engaging with" Congress to "promote the timely availability of affordable, high-quality generic drugs and biosimilars"); *see also* H.R. Rep. No. 114-190, pt. 1, at 100–04 (2015) (noting that extension of exclusivity period for orphan drugs "could delay the timing of market entry by lower-priced generic drugs or biosimilars"); 162 Cong. Rec. S3862 (daily ed.June 14, 2016) (statement of Sen. Leahy) (introducing a bill to address "delays of generic drugs and biosimilar biological products"); 162 Cong. Rec. S6714–15 (daily ed. Dec. 5, 2016) (legislation proposed by Sens. Leahy, Grassley, Klobuchar, and Lee containing two references to "generic drugs and biosimilar biological products").
[44] 82 Fed. Reg. at 56,417.
[45] *Id.*
[46] For example, statutory provisions encouraging "generic substitution" cannot be safely or sensibly read to encompass biosimilars. *E.g.*, 42 U.S.C. § 1395w-111(g)(5)(B)(i); *id.* § 1395w-151(a)(7).
[47] *Sorenson v. Sec'y of Treas. of U.S.*, 475 U.S. 851, 860 (1986) (quoting *Helvering v. Stockholms Enskilda Bank*, 293 U.S. 84, 87 (1934)); *see also, e.g.*, *Taniguchi*, 566 U.S. at 571 (applying rule to give same meaning to "interpreter" in different provisions of Court Interpreters Act); *Gustafson v. Alloyd Co.*, 513 U.S. 561, 568 (1995) (holding that "prospectus" in Securities Act of 1933 "should be construed, if possible, to give it a consistent meaning throughout the Act"); *Dep't of Revenue of Or. v. ACF Indus., Inc.*, 510 U.S. 332, 342 (1994) (holding that "property subject to a property tax levy" in Railroad Revitalization and Regulatory Reform Act of 1976 "must carry the same meaning" in various provisions of the Act); *Sullivan v. Stroop*, 496 U.S. 478, 484 (1990) (applying rule to give same meaning to "child support" in related statutes).

To be sure, the presumption that a given term carries a consistent meaning throughout a statute is not "effectively irrebuttable" and yields when there is evidence that the term was "employed in different parts of the act with different intent."[48] Here, however, there is no evidence that Congress intended for "generic drug" to include biosimilars solely for the cost-sharing provisions in Part D. On the contrary, CMS's proposed change in the definition of "generic drug" cannot be reconciled with Congress's use of the term and the distinct statutory and regulatory schemes for biosimilars and generic drugs. Moreover, the distinctions between small-molecule drugs and biologic products—discussed in detail below--that led Congress to differentiate between generic drugs and biosimilars in other contexts are equally present in the cost-sharing provisions. As CMS appears to acknowledge, the cost-sharing provisions create a financial incentive for patients to choose a generic product over the reference listed drug, given that both are therapeutically equivalent. But a non-interchangeable biosimilar has not been shown to be substitutable for the reference product, and Congress should not be presumed to have ignored this fact.

III. Expanding the definition of "generic drug" to include biosimilars is contrary to FDA's science-based regulatory scheme.

The proposed CMS rule runs contrary to the FDA regulation of biosimilars and generics and the underlying scientific distinctions between the products, by creating an economic incentive for patients to switch between a reference product and a non-interchangeable biosimilar. More broadly, the proposed rule would create confusion and increase the likelihood of inadvertent switching between products that have not been found interchangeable by suggesting, incorrectly, that a non-interchangeable biosimilar is substitutable for the reference product.

In the preamble to the proposed rule, CMS appropriately recognizes that generic drugs and biosimilars are subject to different FDA approval requirements and that treating them as the same in all contexts "would incorrectly signal that CMS has deemed [non-interchangeable] biosimilar biological products to be therapeutically equivalent."[49] For this reason, CMS proposes to include biosimilars in the definition of "generic drug" only for the purposes of certain Part D cost-sharing provision.[50]

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[48] *Envtl. Def. v. Duke Energy Corp.*, 549 U.S. 561, 574 (2007) (quoting *Atl. Cleaners & Dyers v. United States*, 286 U.S. 427, 433 (1932)).

[49] 82 Fed. Reg. at 56,417.

[50] *Id*. We note that CMS has taken very similar positions regarding the importance of distinguishing between generics and biosimilars in its recent rulemaking regarding the reimbursement scheme for biosimilars under Medicare Part B. *See* Final Rule, Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B for CY 2018; Medicare Shared Savings Program Requirements; and Medicare Diabetes Prevention Program, 82 Fed. Reg. 52,976, 53,185 (Nov. 15, 2017) ("We believe that many commenters continue to misunderstand our position on the relationship between biosimilar biological products and generic drugs, that is, we distinguish between the two. . . . . [W]e appreciate[] the complexity of these products and the potential differences in the clinical utilization of biosimilar biological products when they are being used to treat individual patients."). *See also id.* at 53,184. (" The commenters noted that biosimilars are similar, but not identical, to their reference products, and that as a result of potentially subtle differences, they may have different therapeutic and adverse effects on patients, requiring clinical as well as payment distinctions between the products. These commenters believed that Medicare payment policy that treats biosimilars like generic drugs by grouping them for payment would lead to prescribing choices based on cost rather than clinical considerations. . . . [S]ome commenters believed that grouping products for payment could be understood by clinicians and patients that the products could

However, this limitation does not cure the problems created by the proposed rule, namely that it may provide an incentive for a patient to switch from a reference product to a product where the risk of alternating or switching between the reference and the biosimilar has not been demonstrated under the statutory interchangeability standard. We recognize that CMS seeks to "reduce costs to both Part D enrollees and the Part D program."[51] But doing so by "improv[ing] enrollee incentives to choose" non-interchangeable "follow-on biological products over more expensive reference biological products" [52] is contrary to the FDA regulation of non-interchangeable biosimilars and the scientific distinctions between biologics and small-molecule drugs.

More broadly, even with its limited scope, the proposal to add biosimilars to the definition of "generic drug" is likely to create the misimpression that a non-interchangeable biosimilar is therapeutically equivalent to its reference product in the same way that a small-molecule generic drug product is therapeutically equivalent to its reference listed drug. We appreciate that CMS narrowed its treatment of biosimilars as generics to the Part D cost-sharing provisions to avoid "causing any confusion or misunderstanding that CMS treats follow on biological products as generic drugs in all situations" or "incorrectly signal[ing] that CMS has deemed [non-interchangeable] biosimilar biological products to be therapeutically equivalent."[53] But any policy proposal that would put the CMS definition of "generic drug" in direct conflict with the FDA regulatory schemes for generic drugs and biosimilars is likely to create confusion and mislead. Such confusion could cause patients, caregivers, and pharmacists to regard all biosimilars—even non-interchangeable biosimilars—as interchangeable with the reference product (or vice-versa). That misimpression could lead to an inadvertent switch or substitution of products that are not therapeutically equivalent.

IV. Biosimilars may not always be the lowest cost option.

CMS refers to biosimilars as "lower cost alternatives" in the preamble and states that it believes its proposed revision to the definition of "generic drug" will "improve enrollee incentives to choose follow-on biological products over more expensive reference biological products, and will reduce costs to both Part D enrollees and the Part D program."[54] However, it is not guaranteed that a biosimilar will in fact always be the "lower cost alternative" and thus, in cases where the biosimilar's net cost is not lower than that of the reference product, the intended cost savings to the Medicare Part D program could turn into cost increases. For example, a $1,000 reference product with a 25% ($250) rebate would result in a lower net cost to the program ($750) than at $900 biosimilar product (10% discount relative to the reference product) with a 10% ($90) rebate, which would result in a net cost to the program of $810.

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be interchangeable. . . . . Response: . . . . We discussed these issues, including differences between small molecule drugs and biologicals (including biosimilars), generic drugs, and interchangeability in the 2016 final rule. However, . . . we have become increasingly concerned about the relationship between cost, prices and competition; specifically, many commenters' continued unease regarding the effects of our payment policy on patient and provider choices, as well as the biosimilar marketplace.").

[51] 82 Fed. Reg. at 56,417.

[52] *Id.*

[53] *Id.*

[54] *Id.*

Some data may also suggest that switching to a "lower cost" medication might not necessarily reduce overall health care expenses. For example, according to one reported retrospective analysis of 2011-2015 insurance claims data, Crohn's Disease patients who switched from their current therapy to another medicine experienced a more than 100% greater increase in non-drug spending than Crohn's patients who remained on their current therapy ($2,072 vs. $4,499); Multiple Sclerosis (MS) patients who switched from current therapy to another medicine experienced a greater increase in non-drug spending as compared to patients that remained on current therapy ($1,766 vs. $4,362).[55]

Expedited Substitutions of Certain Generics and Other Midyear Formulary Changes

AbbVie agrees with CMS's decision not to permit immediate midyear substitution for biosimilars. As the preamble to the proposed rule explains, "CMS currently considers biosimilar biological products more like brand name drugs for purposes of transition or midyear formulary changes because they are not interchangeable" with the reference product.[56] CMS recognizes that treating biosimilars as generic drugs and allowing midyear substitution could "jeopardize Part D enrollee safety and may generate confusion in the marketplace through conflation with other provisions due to the many places in the Part D statute and regulation where generic drugs are mentioned."[57] We support CMS's current exclusion of biosimilars from immediate midyear substitution because we believe it appropriately distinguishes between generic drugs and biosimilars in a way that is consistent with existing law.

Direct Notice of Midyear Formulary Changes

However, with respect to midyear formulary changes that do occur, we believe that CMS should continue to require, not merely encourage, plan sponsors to provide direct notice to Part D enrollees who are affected by these changes. In the proposed rule, CMS "proposes to add a new paragraph (b)(5)(iv) to § 423.120 to permit Part D sponsors to immediately remove or change the preferred or tiered cost-sharing of brand name drugs and substitute or add therapeutically equivalent generic drugs provided specified requirements are met" (e.g., the generic drug "must be offered at the same or lower cost-sharing and with the same or less restrictive utilization management criteria originally applied to the brand name drug").[58] Rather than requiring direct notice of these changes, CMS proposes to require only that the Part D sponsors provide enrollees general notice that certain generic substitutions could occur without additional advance notice. We are concerned with CMS's proposed changes and believe that, especially where these changes may take place without CMS approval, as proposed, enrollees should still receive direct notice of such changes. CMS has long taken a pro-beneficiary position regarding communications with a Part D plan, and consistent with this approach, CMS should require direct notice of any mid-year formulary changes, even if those changes are to take effect more

[55] *Cost-Motivated Treatment Changes & Non-Medical Switching*. Institute for Patient Access, August 2017.
[56] 82 Fed. Reg. at 56,417.
[57] *Id.*
[58] 82 Fed. Reg. at 56413.

expediently as CMS proposes. As the agency looks for ways to further empower beneficiaries, providing sufficient information on benefits is critical.

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Again, thank you for this opportunity to comment on these important issues for the Part D program and enrollees. Please contact Ashley Flint (ashley.flint@abbvie.com or 202-383-9661) if you have any questions. We look forward to continuing to work with CMS on these and other issues moving forward.

Sincerely,

Ashley Flint
Director, Federal Policy