April 1, 2016

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

Re: **Docket No. FDA-2015-P-4935; Comments of the Generic Pharmaceutical Association (GPhA) and the Biosimilars Council in Opposition to the AbbVie Citizen Petition Regarding FDA Standards for Interchangeability Under the Biologics Price Competition and Innovation Act**

Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) and the Biosimilars Council (Council) is submitting these comments in opposition to the Citizen Petition (CP) submitted by AbbVie, Inc. (AbbVie) requesting the Food and Drug Administration (FDA) to convene a Part 15 hearing on, and subsequently establish scientific standards for, interchangeability determinations under the Biologics Price Competition and Innovation Act of 2009 (BPCIA).[1] Because AbbVie's requests are (a) inconsistent with the relevant statutory requirements, (b) scientifically unjustified, and (c) designed primarily to delay and discourage the development and approval of safe and effective interchangeable biologics, which will limit patient access to these important products contrary to the intent of the BPCIA, FDA should summarily deny the AbbVie petition.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Generics represent greater than 88% of all prescriptions dispensed in the U.S., but only 28% of expenditures on prescription drugs. GPhA is the sole association representing America's generic pharmaceutical sector in the United States. The Council, a division of GPhA, works to ensure a positive regulatory, reimbursement, political and policy environment for biosimilar products, and will educate the public and patients about the safety and effectiveness of biosimilars. Areas of focus include education, access, the nascent regulatory environment, reimbursement and legal issues. Member organizations include any company or stakeholder organization working to develop biosimilar products with the intent to compete in the U.S. market.

AbbVie's CP seeks to impede the development and approval of interchangeable biological products by asking FDA to impose overly-stringent, standards to establish interchangeability that are neither required by the statutory language nor justified by sound science. The BPCIA provides FDA with broad discretion to establish interchangeability requirements on a case-by-case basis consistent with the biological product under review, the

[1] *See* Docket No. FDA-2015-P-4935, AbbVie Inc. Citizen Petition (December 16, 2015) ("AbbVie Petition").

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evolving science and the purpose of the BPCIA to increase patient access to safe, effective and affordable biosimilar and interchangeable biological products. AbbVie's CP, by contrast, is a thinly disguised attempt to subvert these goals by delaying the issuance of FDA guidance on interchangeability, and seeking to impose unrealistic and unnecessary scientific standards on interchangeability determinations. This not only will create significant disincentives to the development of interchangeable biologics but, more importantly, will impair patient access to affordable alternatives to brand name biologics, contrary to Congressional intent. For the reasons discussed in more detail below, FDA thus should summarily reject AbbVie's CP.

A Part 15 Hearing Is Unnecessary and Would Only Serve to Further Delay the Issuance of FDA Guidance on Interchangeability

As an initial matter, FDA should deny AbbVie's request to convene a Part 15 hearing to permit interested parties to present information and views regarding the interchangeability of biological products. Although not stated as such, if FDA were to convene a Part 15 meeting they would unnecessarily delay issuance of guidance on interchangeability until after this meeting so that feedback from the meeting could be considered. Simply put, the request for convening a Part 15 meeting is a thinly veiled attempt to delay issuance of draft guidance on interchangeability.

As AbbVie readily admits, FDA already has convened two public meetings to discuss the implementation of the BPCIA, the first in 2010 and the second in 2012. Although AbbVie contends that these meetings did not address the issue of interchangeability, AbbVie's contention is patently false.[2] For example, in its notice regarding the first public meeting, FDA explicitly solicited comments on two issues that are directly related to interchangeability:

1. "What factors should the agency consider in determining whether a proposed interchangeable biological product can be 'expected to produce the same clinical result as the reference product in any given patient?'"; and

2. "What factors should the agency consider in evaluating the potential risk related to alternating or switching between use of the proposed interchangeable biological product and the reference drug or among interchangeable biological products?"[3]

Likewise, FDA solicited and received comments on interchangeability at its second public meeting held in 2012. Although AbbVie suggests that a discussion of interchangeability was deferred at that meeting because interchangeability was "currently under consideration for

[2] AbbVie Petition, at 20 ("Questions regarding the BPCIA's interchangeability provisions were largely left for another day.").
[3] 75 Fed. Reg. 61487, 61499 (Oct. 5, 2010).

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future guidance,"[4] one of the two primary goals of the second meeting was, in fact, to solicit public input regarding "the Agency's priorities for development of *future policies regarding biosimilars*."[5] In other words, FDA specifically solicited input on "future guidance," including its planned guidance regarding interchangeability. This is confirmed by the fact that "many presenters [at the public hearing] spoke to the issues surrounding implementation of interchangeability" and FDA received written comments regarding interchangeability.[6] AbbVie's contention that these meetings did not address interchangeability thus is not credible.

Consequently, a third public meeting to discuss interchangeability is unnecessary and would serve only to delay the issuance of FDA guidance on interchangeability. Given the strong interest by the biotechnology community to develop interchangeable biologics and the urgent need for sponsors to begin planning and executing clinical trials for interchangeable biological products, it is critical that FDA move forward as expeditiously as possible with issuance of its long-awaited guidance on interchangeability. Further delays could have a strong chilling effect on the development of lower-cost, safe and effective interchangeable biologics.

Moreover, there will be ample opportunity for stakeholders to provide input to FDA during the guidance development process. GPhA and the Council anticipates that, like its other guidance documents implementing the BPCIA, FDA will follow its Good Guidance Practice (GGP) regulations by issuing an interchangeability guidance in draft form before finalizing it.[7] This will provide an opportunity for interested parties, including AbbVie, to provide comments to FDA on its proposed interchangeability standards without unnecessarily delaying implementation of the BPCIA's interchangeability provisions. It also will provide helpful context against which stakeholders can better frame their comments. Accordingly, FDA should deny AbbVie's request to convene a Part 15 meeting and instead move ahead expeditiously with the issuance of its planned guidance document on interchangeability.

The BPCIA Clearly and Explicitly Permits Applicants to Obtain Interchangeability Determinations Based Upon Less Than All Indications or Conditions of Use for Which the Reference Product Is Licensed

FDA also should deny AbbVie's request to impose a requirement that all indications be explicitly studied prior to granting an interchangeability designation. AbbVie's request is inconsistent with both the statutory language, which grants FDA broad discretion to determine interchangeability on a case-by-case basis, as well as fundamental principles of sound science.

In its CP, AbbVie argues that FDA may designate a biosimilar as "interchangeable" to a reference product (RP) only when it has been shown to be interchangeable with respect to *every* indication approved for the RP. AbbVie argues that this requirement should apply even if the

[4] AbbVie Petition at 20 n. 75.
[5] 77 Fed. Reg. 12853, 12854 (March 2, 2012) (emphasis added).
[6] *See* Amgen Comments, FDA-2011-D-0618, p.9 (May 25, 2012).
[7] 21 C.F.R. § 10.115(g).

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biosimilar applicant is not seeking licensure of one or more of those indications. Thus, if the RP is approved for six indications but the biosimilar applicant is seeking licensure and an interchangeability determination for only three of those indications, AbbVie argues that the applicant nevertheless must affirmatively demonstrate interchangeability with respect to all six indications, presumably through separate clinical trials. AbbVie argues that this is necessitated by the nature of biological products, which are more complex than small molecule drugs and carry heightened risks of immunogenicity, which can differ from product to product and patient to patient. AbbVie also argues that this result is required by the explicit statutory language of the BPCIA, which requires interchangeability to be demonstrated with respect to "any given patient." According to AbbVie, the term "any given patient" means all patients for which the RP is approved. For the reasons discussed below, AbbVie's scientific and legal arguments are flawed.

A. AbbVie's Interpretation Is Inconsistent With the Statutory Language

The main problem with AbbVie's legal argument is that it cherry-picks an isolated phrase from the BPCIA and its legislative history and imbues it with a meaning that the language cannot support and that is inconsistent with the rest of the statute. As such, AbbVie's interpretation violates the bedrock principle of statutory construction that a provision cannot be read in isolation but instead must be interpreted in context, taking into account not only the text itself but also the structure and purpose of the statute as a whole.[8]

In this case, AbbVie mistakenly reads the phrase "any given patient" in isolation to mean "any patient population for which the RP is approved." When read within the context of the entire statute, however, it becomes clear that "any given patient" refers not to the RP's indications but rather to the indications and patient populations for which the biosimilar applicant is seeking licensure as an interchangeable biological product. Contrary to AbbVie's suggestion, the phrase "any given patient" thus does <u>not</u> speak to the data requirements for establishing interchangeability. As discussed further below, Congress intentionally left the exact data requirements for interchangeability broad and open-ended, thereby granting FDA wide discretion to calibrate data requirements on a case-by-case basis based upon the particular biological product under review.

As an initial matter, it is important to emphasize that even reading the term "any given patient" in isolation, as AbbVie does, there is no basis to assert that it must refer to all patients for whom the RP is approved. In isolation, the phrase is vague and could just as easily refer to the patients for whom the biosimilar applicant is seeking an interchangeability determination. In fact, this latter interpretation is the most natural, particularly since the entire provision is focused on interchangeability determinations *for the proposed biosimilar product*. Even examining the term "any given patient" in isolation, therefore, AbbVie's interpretation is not supported.

[8] *Robinson v. Shell Oil Co.*, 519 US 337 (1997); *Stat-Trade Inc. v. FDA*, 869 F. Supp. 2d 95, 102 (D.D.C. 2012); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998).

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AbbVie argues for a broader interpretation by likening the phrase "any given patient" to the saying "any given Sunday," but this analogy serves only to highlight the key problem with AbbVie's interpretation, *i.e.*, AbbVie interprets the term in isolation, removed from the context in which it is used. The term "any given Sunday" was coined by former National Football League commissioner Bert Bell, who often said that "on any given Sunday, any team in the NFL can beat any other team." When read in context, therefore, the term "any given Sunday" does not refer broadly to any and all Sundays during the calendar year, but instead is limited to those Sundays that fall within the NFL football season. Likewise, the term "any given patient" found in the BPCIA's interchangeability provisions must be read in the context of the statute as a whole. When this is done, it becomes clear that the phrase refers not to any and all patients generally, or even to any and all patients for whom the RP is approved as biosimilar (as AbbVie contends), but rather only to those indications and patient populations for which the applicant is seeking an interchangeability determinations for the biosmilar.

This more limited interpretation of the term "any given patient" is buttressed by the structure and purpose of the BPCIA. For example, several other BPCIA provisions make clear that a biosimilar applicant can seek an interchangeability determination for less than all the indications for which the RP was approved. Indeed, this is set forth explicitly in the BPCIA's exclusivity provision, which grants approximately one-year of exclusivity to the first biosimilar that is determined to be interchangeable to a RP "for any condition of use."[9] This provision clearly indicates that Congress intended biosimilar applicants to seek, and FDA to award, interchangeability determinations for less than all the conditions of use for which the RP has been approved.

This is further confirmed by the biosimilarity standards established in the statute, which permit an applicant to obtain licensure as a biosimilar for "1 or more appropriate conditions of use for which the reference product is licensed."[10] AbbVie asserts that this provision actually supports its interpretation, since the interchangeability standards do not include similar language allowing carve-outs for certain conditions of use. AbbVie, however, conveniently ignores the fact that this carve-out provision for biosimilars is explicitly incorporated into the interchangeability standard. In fact, the very first requirement for an interchangeability determination is that the biological product must be "biosimilar to the reference product."[11] Consequently, far from creating a distinction between biosimilars and interchangeable biological products with respect to carve-outs, Congress explicitly incorporated the biosimilar carve-out provision directly into the interchangeability standards.

Since applicants are permitted to request and receive biosimilarity and interchangeability determinations for less than all of the RP's indications, it is reasonable to assume that Congress intended the data requirements necessary to support such licensure to be similarly limited to the

[9] 42 U.S.C. § 262(k)(6).
[10] 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc).
[11] In order to be interchangeable, a biological product must be "biosimilar to the reference product." Id. § 262(k)(4)(A)(i).

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indication or indications for which licensure is being sought. This, in fact, is how virtually every other pre-approval pathway administered by FDA functions: applicants are required only to submit data that supports the safety and effectiveness of the indications for which they are seeking approval.[12] In those rare situations in which additional data for other indications are required, such as pediatric testing for certain new drugs, Congress states the exception clearly and unambiguously.[13]

In this case, however, AbbVie contends that the BPCIA contains this highly unusual requirement for testing in indications for which the applicant is not seeking approval, and further, that this requirement is communicated in its entirety in the phrase "any given patient." As noted above, when read in context, this phrase means "any patient population for which the applicant is seeking an interchangeability determination," i.e., the opposite of what AbbVie contends. But even if one were to ignore the context in which the phrase appears in the statute, AbbVie's interpretation has an additional problem: Congress "does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes."[14]

In this case, the phrase "any given patient" is just such a statutory "mousehole." As noted above, when read in isolation, the phrase is, at best, vague. Accordingly, it cannot function as the vehicle by which Congress seeks to impose new, unusual and highly burdensome testing requirements on interchangeable biological products, particularly when those requirements run counter to the intent of Congress to create an *abbreviated* approval pathway for biosimilars and interchangeable biological products. If Congress had intended to impose the highly unusual testing requirements for interchangeability that AbbVie advocates, it would have done so in clear and unambiguous terms, not through means of the vague, ancillary and, at most, highly ambiguous term "any given patient."

In fact, the legislative history indicates that Congress considered adding the exact testing requirement requested by AbbVie – and doing so clearly and unambiguously – but decided to drop that requirement when it passed the BPCIA. In particular, a bill introduced by Rep. Anna Eshoo in 2008 included the following interchangeability requirement:

> "the biological product … can be expected to produce the same clinical result as the reference product in any given patient *for each*

[12] *See Ass'n Amer. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 210 (D.D.C. 2002) (agreeing with plaintiffs that "FDA has no authority to require manufacturers to … conduct studies of drug uses for which they do not intend to seek approval.").
[13] *See, e.g.*, 21 U.S.C. § 355c. It is worth noting that even the pediatric testing requirements under the Pediatric Research Equity Act are limited to pediatric uses of the adult indications for which the applicant is seeking approval.
[14] *Whitman v. Amer. Trucking Assns*, 531 U.S. 457, 468 (2001); *American Bar Ass'n v. FTC*, 430 F.3d 457, 467 (D.C. Cir. 2005).

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> *condition of use prescribed, recommended, or suggested in the labeling of the reference product.*"[15]

When Congress ultimately passed the BPCIA in 2009, however, it dropped the italicized language quoted above. Congress thus knew how to explicitly require testing "for each condition of use prescribed, recommended, or suggested in the labeling of the reference product" but chose not to do so when it enacted the BPCIA.

Although legislative history is notoriously difficult to interpret, the history of the Eshoo bill strongly suggests that Congress dropped the italicized language because it did not believe the broad testing requirement advocated by AbbVie was necessary. At the very least, it significantly undercuts the arguments about legislative history set forth in the AbbVie CP. Indeed, AbbVie totally ignores the above language in the Eshoo bill in its discussion of legislative history even though it addresses the precise issue raised in AbbVie's petition. This omission is surprising – and highly troubling – and makes AbbVie's discussion of the legislative history incomplete and misleading.[16] When the Eshoo bill is considered, it becomes clear that Congress specifically considered – and just as specifically rejected – the very requirement that AbbVie now asks FDA to impose via guidance.[17]

In sum, FDA should reject AbbVie's CP because it is inconsistent with the clear statutory language. Although AbbVie attempts to support its interpretation by cherry-picking isolated portions of the BPCIA and the legislative history, its interpretation falls flat when considered within the context of the entire statute and the full legislative history. Because FDA is required to follow Congressional intent, it should reject as inconsistent with the clear statutory language and relevant Congressional intent AbbVie's attempt to resurrect a requirement that Congress itself considered but ultimately rejected.

B. AbbVie's Request Is Inconsistent with Sound Science

AbbVie's attempt to impose an overly strict clinical trial requirement as a mandatory component supporting interchangeability decisions not only conflicts with the clear statutory language, as discussed above, but also is inconsistent with sound science. As discussed further below, given the broad range of biological products subject to the BPCIA, FDA must have broad discretion to make interchangeability determinations on a case-by-case basis in accordance with

[15] H.R. 5629, § 101(a)(2), 110th Cong., 2nd Sess. (2008) (proposed 42 U.S.C. § 262(k)(4)(A)(i)(II)) (emphasis added).

[16] Pursuant to FDA regulations, a Citizen Petition is required to include "representative information known to the petitioner which is unfavorable to the petitioner's position." 21 C.F.R. § 10.30(b)(3). Although AbbVie identifies the Eschoo bill in a string citation in a single footnote, it fails to mention that the italicized language above was included in the bill and later dropped. *See* AbbVie Petition at 14 n. 58.

[17] Although AbbVie focuses on language in an earlier bill that was ultimately dropped, it is not clear that that language permitted a "selective showing," as AbbVie contends. On the contrary, it is likely that the language describing "conditions of use for which both products are labeled" refers to *all* conditions of use for which either product is licensed. If so, the fact that this language was dropped from the final version of the BPCIA is consistent with the dropping of similar broad language in the Eshoo bill.

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its scientific expertise and judgment. This not only enables FDA to calibrate relevant testing requirements to the complexity and risks presented by the proposed interchangeable biological product but also allows FDA to avoid unnecessary and potentially unethical human testing.[18]

As AbbVie itself acknowledges, the complexity of biological products subject to regulation under the BPCIA varies widely, and this affects the type and amount of data required to demonstrate both biosimilarity and interchangeability. Moreover, while most proteins have an increased risk of immunogenicity compared to small-molecule drugs, those risks also are subject to wide variation based upon both product-specific factors and patient-specific factors.[19] As AbbVie states, "[t]his means, in essence, that immunogenicity can vary from patient to patient, from population to population, and from indication to indication."[20]

While it is true that immunogenicity risks may be highly variable for biologics, this does not mean that, as a scientific matter, it is necessary to conduct clinical and/or immunogenicity tests in every indication for which the RP is licensed – or even in every indication for which the 351(k) applicant is seeking licensure. Rather, depending upon a wide variety of factors, including, *inter alia*, the complexity of the products, the degree to which they can be characterized by analytical testing, the level of structural similarity between the biosimilar and RP, the known mechanism or mechanisms of action, the history of clinical use, the known risks of immunogenicity and the patient populations involved, it may be feasible to extrapolate clinical immunogenicity testing from one indication to others. Indeed, FDA's existing scientific guidance permits applicants to extrapolate between indications where appropriate, including with respect to immunogenicity assessments. According to FDA, if a sponsor seeks to extrapolate immunogenicity findings for one condition of use to others, the sponsor should consider using a study population and treatment regimen that are adequately sensitive for predicting a difference in immune response between the proposed biosimilar and the reference product across conditions of use.[21] Usually, this will be the population and regimen for the RP for which development of immune responses with adverse outcomes is most likely to occur.[22]

Although FDA's guidance regarding extrapolation is directed primarily at biosimilarity determinations, as a scientific matter, there is no reason it should not apply equally to interchangeability.[23] AbbVie itself tacitly acknowledges this fact when discussing product changes to the RP after an interchangeability determination. In particular, AbbVie states that

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[18] 42 U.S.C. § 262(k)(2)(A)(ii) (permitting FDA to waive certain testing requirements if, in its discretion, they are unnecessary for a particular biological product).
[19] FDA, *Guidance for Industry: Immunogenicity Assessments for Therapeutic Protein Products*, at 2 (Aug. 2014).
[20] AbbVie Petition, at 7.
[21] FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 17 (April 2015).
[22] *Id.*
[23] This is also consistent with FDA's treatment of generic drugs approved under the Hatch-Waxman provisions. In the generic drug context, "[i]t is the Agency's policy to require only those studies necessary to assess bioequivalence – if bioequivalence can be shown for a multi-indication drug with a comparative clinical trial in just one indication, the other indications need not be studied." FDA Response to Aldara Petition, FDA-2009-P-0364, p. 5 (Jan. 26, 2010).

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when the RP is approved for a new indication or condition of use after FDA already has determined one or more biosimilars to be interchangeable, the "previously issued interchangeability determination should not be disturbed absent significant scientific questions regarding the continuing validity of the determination following a product change."[24] In other words, AbbVie believes the previously issued interchangeability determination should be extrapolated to the newly approved indication(s). GPhA and the Council agree that extrapolation is appropriate in this post-licensure scenario but also believes extrapolation is equally applicable to pre-licensure interchangeability determinations. AbbVie, in fact, has provided no scientific reason for limiting extrapolation to post-licensure interchangeability determinations, and neither GPhA nor the Council is aware of any. Consequently, AbbVie's admission with respect to post-interchangeability determination product changes not only severely undercuts its purported safety concerns generally but also supports application of a similar standard to initial interchangeability determinations.

Moreover, AbbVie's request is inconsistent with FDA policy regarding manufacturing changes to innovator products. Such manufacturing changes can result in changes in the quality attributes and functionality of the innovator product. FDA nevertheless permits such changes if the pre- and post-change products are shown to be "highly similar," the same standard used for a biosimilarity determination. Under current FDA policy, the pre- and post-change products are presumed to be interchangeable in terms of safety and effectiveness in all indications, usually based on analytical and other non-clinical testing. Multiple examples of such changes have been identified in Europe, where the EMA publishes European Public Assessment Reports.[25] It is reasonable to assume that many of the products discussed in the European-specific articles are also licensed in the US, with the same manufacturing changes reviewed and approved by the FDA. Contrary to AbbVie's assertion that "highly similar" biologics have the potential for loss of tolerance and efficacy with switching, FDA permits these "highly similar" versions of the innovator product to remain on the market together, where switching can occur, without any concerns about the safety or efficacy of the marketed innovator products.

Finally, giving FDA discretion to calibrate the information necessary to support an interchangeability determination on a case-by-case basis allows FDA to avoid requiring unnecessary and potentially unethical clinical trials in one or more patient populations. During Congressional hearings on biosimilar legislation, Dr. Janet Woodcock testified that "[w]here trials aren't needed, it is … of questionable ethics to repeat them. So uses of human subjects for trials that are not needed or *done simply to check a box on a regulatory requirement* are not

[24] AbbVie Petition at 15.
[25] C Schneider. "Biosimilars in rheumatology: The winds of change." Ann Rheum Dis (2013) 72(3): 315-318; Balázs Vezér, Zsuzsanna Buzás, Miklós Sebeszta & Zsombor Zrubka (2016): Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents, Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1145579. Available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (accessed March 16th, 2016)

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desirable."[26] This is consistent with the Agency's approach to clinical testing generally, which seeks to "avoid requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health."[27] In this case, the clear intent of AbbVie's proposal is to slow the process for licensure of interchangeable biological products and increase drug costs by requiring unnecessary and potentially unethical clinical studies. Because there is no corresponding scientific need or public benefit to this proposal, FDA should summarily reject this transparent regulatory-box-checking exercise.

The Heightened Interchangeability Standards Proposed By AbbVie Are Inconsistent With the Intent of the BPCIA to Encourage Development of and Provide Increased Patient Access to Lower-Cost, Safe and Effective Interchangeable Biologics

In addition to requesting interchangeability testing in each indication for which the RP is approved, AbbVie argues that FDA should apply extremely strict standards to interchangeability determinations. For example, AbbVie argues that use of the term "any given patient" in the BPCIA requires FDA to base interchangeability determinations on a different statistical design than a population level approach, which FDA uses for bioequivalence determinations. It is worth noting that, under AbbVie's proposed interpretation, the phrase "any given patient" is imbued with a wide variety of meanings: on the one hand, requiring testing in all indications for which the RP is approved while on the other hand, prescribing the statistical approach FDA must use when analyzing those tests. This simple phrase, however, cannot possibly serve these multiple and varied functions. The fact that AbbVie presses it into service in this way – in essence attempting to hide an entire herd of elephants in a statutory mouse hole – serves to underscore the lack of support within the BPCIA for AbbVie's positions.

Likewise, AbbVie argues that while a biosimilar could be approved even if it has slight differences compared to the RP in the timing or magnitude of clinical response, such differences would bar a finding of interchangeability because of the purportedly more exacting standard established by the "same clinical result" language in the statute. Finally, for products that are administered more than once, AbbVie argues that an applicant will need to establish with "near-certainty" that the risks of switching or alternating are no greater than using the RP alone, which AbbVie states "has implications for study design and statistical method." According to AbbVie, this essentially requires a "full evaluation of safety and effectiveness" in the context of switching. Furthermore, the term "near-certainty" is never mentioned in the BPCIA, regulatory

[26] *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the Subcomm. On Health of the H. Comm. On Energy and Commerce*, 110th Cong., at 53 (statement of Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer, FDA) (emphasis added).
[27] FDA Petition Response, Legacy Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408, at 3 (Oct. 14, 2003).

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guidance or even in any presentation given by FDA on biosimilars. As a regulatory matter, "near-certainty" has no meaning.

The main problem with AbbVie's argument, however, is that it is not supported by the statutory language, which provides FDA with broad discretion to make interchangeability determinations on a case-by-case basis. Under the statute, applicants are required to provide "information … sufficient to show" that a biological product is interchangeable with a RP. Significantly, the statute does not prescribe the type or amount of information required to make any of the specific showings required for an interchangeability determination but instead leaves it to FDA's discretion to determine whether the "information" submitted is "sufficient" on a case-by-case basis depending upon the specific product in question. This means that in some cases, depending upon the product in question and state of the available science, interchangeability could be shown without clinical trials or with only limited clinical testing at least as a statutory matter. Indeed, it is even possible that the data package submitted to establish biosimilarity could be rigorous enough to establish that the biological product also "can be expected to produce the same clinical result as the reference product in any given patient." Congress certainly knows how to require clinical trials when it wants to but it did not do so for interchangeability as it did not do so for a determination of biosimilarity. . Instead, Congress provided FDA with broad discretion to calibrate interchangeability determinations on a case-by-case basis depending on the state of the relevant science and the characteristics of the specific biological product under review. This delegation of scientific judgment to the Agency was intentional and was designed to encourage investment and innovation in the science of biosimilarity and interchangeability.

In its CP, AbbVie counters that Congress intended to require extensive clinical testing as evidenced by its award of exclusivity to the first interchangeable biological product for a given RP. But the limited exclusivity available to interchangeable biological products – not exceeding 1 year after commercial marketing – does not provide an effective incentive to conduct the extensive clinical testing urged by AbbVie, which could be more rigorous and involved than what is required for a full BLA. Rather it encourages investment in improved science (clinical or nonclinical) that could lead to more affordable, high quality, interchangeable biologics.

As a comparison, a full BLA receives 12 years of marketing exclusivity whereas an interchangeable biological product gets, at most, one year. It simply is not rational to suggest that Congress believed it could incentivize extensive clinical research requested with 1/12th of the exclusivity reward. Instead, it is instructive to look at the Hatch-Waxman Act, which was designed to strike a similar balance as the BPCIA. There, Congress provided an exclusivity period for the first generic that is roughly on par with the exclusivity period for interchangeable biological products. Indeed, under the Hatch-Waxman Act, the first generic with a paragraph IV certification receives approximately 1/10th of the exclusivity provided to new chemical entities (i.e., 180-day exclusivity), which is comparable to the 1/12th share granted to the first interchangeable biological product under the BPCIA. Significantly, 180-day exclusivity is granted in exchange for, at most, bioequivalence testing and regardless of whether there is a patent infringement lawsuit. Likewise, first interchangeable exclusivity is designed to reward

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limited nonclinical and/or clinical testing on par with bioequivalence testing, not to incentivize the extensive clinical development programs requested by AbbVie.

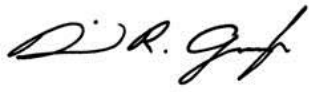
The other major problem with AbbVie's proposal is that it is inconsistent with the underlying purpose of the BPCIA, which is to encourage the development of lower-cost, safe and effective biosimilars and interchangeable biological products and increase access to such products by patients. To do this, Congress created an *abbreviated* approval pathway much like the generic drug approval pathway created by the Hatch-Waxman Act. Both pathways are abbreviated and result in cost savings, in large part, because the clinical and non-clinical testing requirements are limited. Under AbbVie's proposal, however, the testing necessary to demonstrate interchangeability could approach or even exceed that required to obtain approval of a full BLA by incorporating novel standards such as individual rather than population-based analyses and "near certainty" for comparative risk conclusions. This, in turn, would erect significant barriers to the development of interchangeable biological products that, as a practical matter, would serve as an effective deterrent to applicants seeking to use this important licensure pathway.

This, in fact, seems to be the intent behind AbbVie's interchangeability petition, the latest in a long line of petitions designed primarily to impede competition from safe and effective biosimilars and interchangeable biological products and to limit patient access. AbbVie's incentive is clear: to protect its flagship biological franchise, Humira®, which is generating billions of dollars in profit every year. Unfortunately, AbbVie's incentive to obstruct the development and licensure of interchangeable biological products at any and all costs is antithetical to the intent of Congress to create an abbreviated approval pathway that will make affordable, safe and effective biosimilars and interchangeable biological products accessible to patients in the United States. Because AbbVie's proposal is inconsistent with the overriding purpose of the BPCIA and unsupported by the statutory language or sound science, FDA should summarily reject it.

Conclusion

For the reasons set forth above, FDA should deny all aspects of the AbbVie CP. AbbVie's interchangeability testing requests are inconsistent with the relevant statutory requirements and scientifically unjustified. FDA thus should reject this transparent attempt to discourage the development and approval of interchangeable biologics by erecting unnecessary clinical testing requirements, since it would subvert the overarching goal of the BPCIA to increase patient access to safe, effective and affordable biosimilar and interchangeable biological products.

Sincerely,



David R. Gaugh, R.Ph.
Senior Vice President for Sciences and Regulatory Affairs

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