



Your Generics & Biosimilars Industry



May 19, 2017

VIA ELECTRONIC DELIVERY

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-D-0154 for “Considerations in Demonstrating Interchangeability With a Reference Product: Draft Guidance for Industry; Availability;” Comments of the Association for Accessible Medicines and the Biosimilars Council

Dear Sir or Madam:

The Association for Accessible Medicines (“AAM”), formerly known as the Generic Pharmaceutical Association, and the Biosimilars Council (“Council”) (collectively referred to in these comments as AAM), are pleased to provide comments to the Food and Drug Administration (“FDA” or “the Agency”) on the Agency’s Draft Guidance on *Considerations in Demonstrating Interchangeability With a Reference Product* (“Draft Guidance”), which was made publicly available in January 2017. 82 Fed. Reg. 5579 (Jan. 18, 2017) (Docket No. FDA-2017-D-0154). The biotechnology community has a strong interest in developing interchangeable biological products and an urgent need for clarity regarding the standards FDA will apply to the licensure of interchangeable biologics. Consequently, the issuance of FDA’s long-awaited Draft Guidance is an important step toward making safe, effective and accessible interchangeable biological products available to American patients.

AAM 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. AAM is the sole association representing America’s generic pharmaceutical sector in the United States. The Council, a division of AAM, 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 companies or stakeholder organizations working to develop biosimilar products with the intent to compete in the U.S. market.

AAM and the Council support many aspects of the Draft Guidance. For example, we believe it is scientifically and legally appropriate for sponsors to extrapolate data and information supporting interchangeability in one indication or condition of use to other indications or conditions of use. FDA permits extrapolation for purposes of demonstrating biosimilarity and, as a scientific matter, there is

no reason not to apply it equally to interchangeability. It is important to note that the biosimilar and interchangeable approval pathways were intended by Congress to be *streamlined* pathways, and FDA’s licensure requirements should reflect that Congressional intent, consistent with sound science and the broadest possible application of the principles of extrapolation is fitting and proper in the context of interchangeability.

As discussed in more detail below, however, we are concerned that several recommendations in the Draft Guidance impose unnecessary scientific standards on interchangeability determinations and/or are inconsistent with the relevant statutory requirements. For example, we strongly oppose FDA’s “expect[ation] that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product’s licensed conditions of use.”¹ The agency, however, lacks the authority to require sponsors to conduct studies and submit data for conditions of use for which they do not intend to seek licensure. Accordingly, we ask FDA to clarify that a sponsor of an interchangeable biologic need not demonstrate interchangeability in those indications for which it is not seeking licensure. Likewise, with regard to the endpoints for switching studies, we are concerned FDA’s focus on pharmacokinetic and pharmacodynamics endpoints is too narrow and, accordingly, we ask that FDA acknowledge that alternative endpoints may be used when pharmacokinetic or pharmacodynamics endpoints are not appropriate. We believe FDA should allow sponsors flexibility to use appropriate reference products in switching studies and its recommendation of using comparative human factor studies to evaluate the interchangeability of two presentations. In our view, these and other requirements set forth in the Draft Guidance are not scientifically justifiable and inconsistent with the streamlined licensure pathway envisioned by Congress. If finalized, these requirements not only will create significant disincentives for sponsors to develop interchangeable biologics but, more importantly, will significantly impair patient access to affordable alternatives to brand name biologics, contrary to Congressional intent. Consequently, AAM and the Council respectfully request that FDA modify the Draft Guidance as set forth below.

I. AAM and the Council Support FDA’s Proposed General Principles

A. Totality of the Evidence and Stepwise Approach

In the Draft Guidance, FDA indicates that it intends to consider the “totality of evidence” provided by the sponsor when evaluating whether a biological product is interchangeable with the RP. (Draft Guidance at 2) According to the Agency, the data and information necessary to support interchangeability determination likely will vary depending upon a number of factors, including product complexity, product-specific immunogenicity risks, and the extent of functional and comparative characterization. (Draft Guidance at 3-7) FDA thus recommends that sponsors use a “stepwise approach” to generating data and information to address “residual uncertainty” about interchangeability at each step of the development process. (Draft Guidance at 5) This general approach toward demonstrating interchangeability is very similar to the Agency’s approach to demonstrating biosimilarity, which also adopts “totality of the evidence” and “stepwise approach” policies.

¹ FDA Draft Guidance Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry, January 2017, Line 76, page 3

AAM and the Council generally support FDA’s adoption of the “totality of the evidence” standard and “stepwise approach” for making interchangeability determinations. The Biologics Price Competition and Innovation Act of 2009 (“BPCIA”) provides FDA with broad discretion to establish interchangeability requirements on a case-by-case basis consistent with the biological product under review, the evolving science and the purpose of the BPCIA to increase patient access to safe, effective and affordable biosimilar and interchangeable biological products. Under the statute, applicants are required to provide “information ... sufficient to show” that a biological product is interchangeable with a RP. 42 U.S.C. § 262(k)(4). 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. Given the broad range of biological products subject to the BPCIA, FDA must have broad discretion to tailor its scientific decisions appropriately in accordance with its scientific expertise and judgment. We believe that the approach proposed in the Draft Guidance preserves this discretion and will allow the Agency to calibrate interchangeability requirements to the characteristics of the specific biological product under review and the state of the relevant science.

We caution, however, that FDA must use this discretion in a manner that is consistent with the broad purposes of the BPCIA to create a *streamlined* licensure pathway that *increases access* to safe and effective interchangeable biological products. FDA thus should seek to avoid requiring unnecessary data and information that could divert resources and slow the licensure of interchangeable biological products. 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 use of human subjects for trials that are not needed or *done simply to check a box on a regulatory requirement* are not desirable.”² 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 analysis of lengthy studies with inappropriate endpoints (i.e. PK/PD) 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.”³ Accordingly, we urge FDA to ensure that the overarching goals of the BPCIA inform the Agency’s exercise of its broad discretion to make interchangeability determinations.

B. Extrapolation

AAM and the Council also support FDA’s position that sponsors may extrapolate data and information supporting interchangeability in one condition of use to other conditions of use, if justified. As noted above, 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

² *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).

³ FDA Petition Response, Legacy Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408, at 3 (Oct. 14, 2003).

immunogenicity compared to small-molecule drugs, those risks also are subject to wide variation based upon both product-specific factors and patient-specific factors.⁴

Contrary to arguments made by some brand companies,⁵ however, this variation does not mean that, as a scientific matter, that it is necessary for sponsors to conduct clinical and/or immunogenicity testing in every indication for which the RP is licensed or 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 proposed interchangeable product 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 is entirely feasible to extrapolate interchangeability data (including clinical immunogenicity testing) from one indication to others.

This, in fact, is consistent with FDA's existing scientific guidance permitting applicants to extrapolate between indications where appropriate, including with respect to immunogenicity assessments, for purposes of biosimilarity. 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 RP across conditions of use.⁶ 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.⁷ We support the FDA applying the same principles for extrapolation of biosimilarity to extrapolation for interchangeability. As a scientific matter, there is no reason it should not apply equally to interchangeability.⁸ FDA's decision to allow extrapolation in the context of interchangeability determinations is thus consistent with Agency precedent and sound science.

II. FDA Does Not Have Authority to Require Data and Information on Indications or Conditions of Use for Which the Sponsor Is Not Seeking Approval

In the Draft Guidance, FDA states that it expects sponsors to “submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use.” (Draft Guidance at 3) Elsewhere, the Agency acknowledges that sponsors may seek approval for fewer than all conditions of use for which the RP is licensed but nevertheless “recommends” that sponsors “seek licensure for all of the [RP's] licensed conditions of use when possible. (Draft Guidance at 4)

⁴ FDA, *Guidance for Industry: Immunogenicity Assessments for Therapeutic Protein Products*, at 2 (Aug. 2014).

⁵ See AbbVie Inc. Citizen Petition, Docket No. FDA-2015-P-4935, at (December 16, 2015) (“AbbVie Petition”).

⁶ FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 17 (April 2015).

⁷ *Id.*

⁸ 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).

If FDA is proposing a policy that sponsors must submit “data and information” showing interchangeability for all of the RP’s licensed conditions of use even if the sponsor is not seeking licensure for all such conditions of use, we strongly oppose this policy as scientifically unjustified and inconsistent with the relevant statutory requirements. Because such a policy would have the effect of delaying and discouraging the development and approval of safe and effective interchangeable biological products, we respectfully request that FDA (a) explicitly disclaim any such policy, and (b) clarify that a sponsor must provide “data and information” demonstrating interchangeability *only for the indications and conditions of use for which the sponsor is seeking approval*.

It is well-established that FDA does not have authority to require sponsors to conduct studies of uses for which they do not intend to seek approval. In *Ass’n Amer. Physicians & Surgeons, Inc. v. FDA*, for example, the United States District Court for the District of Columbia enjoined FDA from enforcing its Pediatric Rule on the grounds that the Agency had exceeded its authority in adopting the regulation.⁹ The Pediatric Rule sought to require sponsors of certain New Drug Applications (“NDAs”) and supplemental NDAs (“sNDAs”) to conduct testing of their drug products in pediatric patients even if the sponsors were not seeking approval of pediatric indications or labeling. The District Court carefully considered whether Congress had given FDA authority to require such testing but ultimately found none. The Court thus agreed with the plaintiffs that “FDA has no authority to require manufacturers to ... conduct studies of drug uses for which they do not intend to seek approval.”¹⁰

Consequently, the bedrock understanding in every pre-approval pathway administered by FDA is that applicants are required to submit data and information that supports the safety and effectiveness only of the indications for which they are seeking approval. 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.¹¹ Courts generally require clear and unambiguous language because of the natural tendency of agencies to expand their jurisdiction and power. As the D.C. Circuit has explained: “Where the issue is one of whether a delegation of authority by Congress has indeed taken place (and the boundaries of any such delegation ..., Congress can reasonably be expected both to have and to express a clear intent.”¹²

In this case, Congress has not altered, through clear and unambiguous language, the bedrock presumption that sponsors of proposed interchangeable biological products must provide data and information supporting interchangeability only for those indications and conditions of use for which they are seeking licensure. On the contrary, both the statutory language and the structure of the BPCIA indicate that a sponsor can seek an interchangeability determination for less than all the indications for which the RP was approved. For example, the BPCIA grants approximately one-year of exclusivity to the first biosimilar product that is determined to be interchangeable to a RP “for any

⁹ *Ass’n Amer. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002).

¹⁰ *Ass’n Amer. Physicians & Surgeons, Inc.*, 226 F. Supp. 2d 204, 210.

¹¹ *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.

¹² *ACLU v. FCC*, 823 F.2d 1554, 1567 n. 32 (D.C. Cir. 1987); *see also Continental Air Lines, Inc. v. Dept. of Transp.*, 843 F.2d 1444, 1449 n. 4 (D.C. Cir. 1988) (“Congress can reasonably be expected to be quite precise in defining critical jurisdictional terms going to the very power of the agency to regulate.”).

condition of use.”¹³ This provision clearly indicates that Congress intended sponsors to seek, and FDA to award, interchangeability determinations for less than all the conditions of use for which the RP has been approved.

Likewise, the BPCIA permits a sponsor to obtain licensure as a biosimilar for “1 or more appropriate conditions of use for which the reference product is licensed.”¹⁴ Although this carve-out provision is nominally limited to biosimilar products, it applies equally to interchangeable biological products. This is because the very first requirement for an interchangeability determination is that the biological product must be “biosimilar to the reference product.”¹⁵ Accordingly, the biosimilarity standard – including the carve-out provision – is explicitly incorporated into the interchangeability standard. Since applicants are permitted to request and receive interchangeability determinations for less than all of the RP’s indications, it is reasonable to assume – absent express language otherwise – that Congress intended the data requirements necessary to support such licensure to be similarly limited to the indication or indications for which licensure is being sought.

In this case, there is no express language giving FDA clear statutory authority to require sponsors to submit data and information on indications or other conditions of use for which they are not seeking licensure. Nevertheless, in its Citizen Petition, AbbVie argues that the BPCIA gives FDA such authority by means of the phrase “any given patient.” AbbVie’s argument is meritless for at least four reasons.

First, the phrase “any given patient” is vague and does not necessarily even address the issue of which indications or conditions of use must be addressed in a 351(k) application. However, even if it did, there is no basis to assert that it must refer to the indications for which the RP is approved, as AbbVie suggests. The phrase could just as easily refer to the indications for which the sponsor is seeking an interchangeability determination. In fact, given that the entire provision is focused on interchangeability determinations *for the proposed biosimilar product*, this latter interpretation is arguably the most natural.

Because the phrase is vague, 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. As the federal courts have recognized, 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.”¹⁶ In this case, the phrase “any given patient” is just such a statutory mousehole. It thus cannot support AbbVie’s interpretation. On the contrary, 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 phrase “any given patient.”¹⁷

¹³ 42 U.S.C. § 262(k)(6).

¹⁴ 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc).

¹⁵ In order to be interchangeable, a biological product must be “biosimilar to the reference product.” *Id.* § 262(k)(4)(A)(i).

¹⁶ *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).

¹⁷ *ACLU*, 823 F.2d 1554, 1567 n. 32 (“Where the issue is one of whether a delegation of authority by Congress has indeed taken place (and the boundaries of any such delegation . . . , Congress can reasonably be expected both to have and to

Second, AbbVie 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 noted above, when the phrase “any given patient” is read in context with the rest of the BPCIA, including the provisions authorizing labeling carve-outs, it becomes clear that the most natural reading is that the provision is referring to the indications for which the sponsor is seeking an interchangeability determination, not the indications for which the RP is approved. Accordingly, 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.¹⁸

Third, AbbVie’s interpretation conflicts with the available legislative history. Indeed, 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 condition of use prescribed, recommended, or suggested in the labeling of the reference product.*”¹⁹

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 (and apparently incorporated in the Draft Guidance) was necessary.

Finally, AbbVie’s interpretation 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* licensure 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. In this case, requiring data and information on indications or other conditions of use for which the sponsor is not seeking approval would impose approval requirements that, in some ways, exceed those of a full BLA. Even if FDA allows sponsors to use extrapolation to address the unlabeled indications or conditions of use, sponsors would need to submit a thorough scientific justification for such extrapolation. This additional testing and/or information would, in turn, erect significant barriers to the development of

express a clear intent.”); *see also Continental Air Lines*, 843 F.2d 1444, 1449 n. 4 (“Congress can reasonably be expected to be quite precise in defining critical jurisdictional terms going to the very power of the agency to regulate.”).

¹⁸ *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).

¹⁹ H.R. 5629, § 101(a)(2), 110th Cong., 2nd Sess. (2008) (proposed 42 U.S.C. § 262(k)(4)(A)(i)(II)) (emphasis added).

interchangeable biological products that, as a practical matter, would serve as an effective deterrent to applicants seeking to use this important licensure pathway.

In sum, FDA does not have authority to require sponsors to conduct studies or submit data and information regarding uses for which they do not intend to seek an interchangeability determination. Moreover, such a requirement is inconsistent with the intent of Congress to create an *abbreviated* approval pathway that will make affordable, safe and effective interchangeable biological products accessible to patients in the United States. Accordingly, AAM and the Council respectfully request that FDA (a) explicitly disclaim any such policy, and (b) clarify that a sponsor must provide “data and information” demonstrating interchangeability *only for the indications and conditions of use for which the sponsor is seeking approval*.

III. Demonstrating Interchangeability

A. High Structural Complexity

In the Draft Guidance, FDA indicates that product complexity will be one factor considered when determining the data requirements necessary to support a demonstration of interchangeability. (Draft Guidance at 5) Products with a relatively low structural complexity may give rise to less residual uncertainty and thus need less data to support interchangeability than products that have “high structural complexity.” (Draft Guidance at 7)

We generally agree that FDA should calibrate applicable testing and data requirements based upon a wide variety of factors, including product complexity. For this reason, the Draft Guidance should more clearly define the characteristics that FDA will use to determine a product’s complexity. Although FDA provides two examples of a “low structural complexity” product and a “high structural complexity” product, (Draft Guidance at 7) there is a fairly wide gulf between these examples. We thus believe that additional examples of products falling within this continuum and additional explanation of the characteristics that affect a complexity determination would be helpful.

B. Fingerprint-Like Characterization

Likewise, AAM and the Council request additional clarity regarding FDA’s expectations for “fingerprint-like characterization” to support interchangeability. According to FDA, “a fingerprint-like characterization may reduce residual uncertainty regarding interchangeability and inform the data and information needed to support a demonstration of interchangeability, which may lead to a more selective and targeted approach to clinical studies necessary to demonstrate interchangeability.” (Draft Guidance at 6) We agree that the extent of analytical and functional characterization can affect the need for and scope of subsequent clinical trials, if any, under a stepwise, “totality of the evidence” approach to addressing interchangeability.

Because a fingerprint-like characterization represents the most rigorous approach to analytical and structural characterization, we believe industry would benefit from a more detailed understanding of FDA’s expectations. Although the Draft Guidance indicates that additional information regarding

fingerprint-like characterization is available in other guidance documents,²⁰ a description of what fingerprint-like characterization is insufficiently described in other guidance documents. Accordingly, AAM and the Council believe it would be helpful for FDA to provide an explanation of what is meant by fingerprint-like characterization in the Final Interchangeability Guidance and clarify that there are no additional structural and functional characterizations required for interchangeable biologics beyond those required to establish biosimilarity. Moreover, we believe it would be helpful for FDA to further explain how a fingerprint-like characterization could affect the need for and scope of clinical trials supporting interchangeability.

C. Study Endpoints

FDA has proposed that “[t]he primary endpoint in a switching study should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical pharmacokinetics and pharmacodynamics (if available).” However, we believe the requirement for a PK/PD study is not always clinically meaningful or reflective of clinically relevant immunogenicity in all situations or indications. For instance, a PK/PD endpoint will not necessarily be possible for a product intended for intra-ocular administration or for a product that is titrated to a treatment target. In addition, changes in PK or PD may occur due to underlying disease in patients and may not be related to immunogenicity.²¹

Accordingly, FDA should work closely with 351(k) applicants to develop an appropriate study design to generate the data necessary to support an interchangeability determination taking into account the particularities of the product. In some cases, this may be a PK/PD primary endpoint either in patients or healthy subjects, in others, PK/PD may be appropriate secondary endpoints, for others, clinical endpoints may be appropriate. We do not believe there is a “one-size fits all” study design. Thus, AAM and the Council urge that the Final Guidance acknowledge that it will exercise the flexibility inherent in the statute and work with sponsors to tailor endpoints to the relevant examination of the specific product.

D. Postmarketing Surveillance and Studies

In the Draft Guidance, FDA indicates that postmarketing data collected from products first licensed as biosimilars generally would not be sufficient, standing alone, to support a demonstration of interchangeability and that switching studies generally would be necessary. (Draft Guidance at 8) The Agency nevertheless indicates that postmarketing data may reduce residual uncertainty regarding interchangeability and thus could affect the data necessary to support interchangeability. (Draft Guidance at 8) AAM and the Council agree that FDA should consider postmarketing data that may already be available for a biosimilar product as part of the totality of evidence supporting interchangeability.

²⁰ See *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*, at 8 (April 2015); *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*, at 5 (Dec. 2016).

²¹ S Zheng, W Wang and H Zhou. “*Impact of diseases, comorbidity and target physiology on ADME, PK and PK/PD of therapeutic biologics*” in *ADME and Translational Pharmacokinetics / Pharmacodynamics of Therapeutic Proteins: Applications in Drug Development and Discovery*. H Zhou and F-P Thiel eds. (2016) J Wiley NJ.

We are concerned; however, that FDA may **require** some applicants to seek licensure as a biosimilar first in order to generate postmarketing surveillance data to support subsequent licensure as an interchangeable biological product. Although sponsors should be free to utilize a two-step approach for licensure of interchangeable products if they deem it advisable, We does not believe FDA should *mandate* a two-step approach or demand postmarketing surveillance data prior to licensure. Because FDA will have ample postmarketing surveillance data from the RP, the value of additional postmarketing surveillance data from a biosimilar may be minimal. In most cases, we believe that, as a scientific matter, interchangeability determinations can and should be made primarily on the basis of analytical and functional analysis and, where necessary, clinical trials.

Finally, AAM and The Council requests clarification regarding when a postmarketing study may be required. The Draft Guidance states that “there may be situations where a postmarketing study, in addition to postmarketing surveillance data, from the licensed biosimilar product may be needed to address residual uncertainty regarding a demonstration of interchangeability.” (Draft Guidance at 8) We respectfully request that FDA identify the factors that could trigger the need for a postmarketing study as well as the purpose and design characteristics of such as study.

E. Use of Foreign Reference Product

In the Draft Guidance, FDA states that the use of a non-U.S.-licensed comparator product would not typically be appropriate in a switching study and thus that sponsors should use a U.S.-licensed comparator product. (Draft Guidance at 15) FDA argues that there may be “subtle differences” between the U.S.-licensed RP and non-U.S. versions, which would introduce uncertainty as to whether the results observed in a switching study using a non-U.S. version of the RP would be consistent with results observed using the U.S.-licensed RP. (Draft Guidance at 16) FDA thus “strongly recommends” that sponsors conduct switching studies with the U.S.-licensed RP rather than foreign versions.

We believe that FDA’s concerns regarding subtle differences between U.S. and non-U.S. versions of the RP are scientifically unjustified. While it is true that there may be subtle differences between U.S. and non-U.S. versions of an RP, FDA ignores the fact that sponsors already are required to demonstrate that the U.S. and non-U.S. versions are comparable as part of the biosimilarity requirements. Indeed, if a sponsor uses a non-U.S. version of the RP in clinical trials to demonstrate biosimilarity, it is required to establish a three-way bridge between the proposed biosimilar product, the U.S.-licensed RP and the foreign version of the RP based upon analytical and clinical data. This data obtained as a part of the biosimilarity bridge should be adequate and acceptable to support use of a non-U.S.-licensed product sourced from the same market in interchangeability switching studies.

Moreover, as the Agency well knows, the cost of brand biologics in Europe and other foreign markets is typically well below the cost in the U.S. Consequently, an FDA requirement to use the U.S.-licensed RP in switching studies will result in significantly increased development costs that will create strong disincentives for the development of interchangeable biological products. AAM and the Council thus believe that this requirement conflicts with the overarching goals of the BPCIA to establish a *streamlined* licensure pathway that fosters *increased access* to affordable interchangeable biological products. We thus respectfully requests that FDA revise the Draft Guidance to indicate

that, if an adequate bridge is established, sponsors may use a non-U.S.-licensed RP in switching studies to support interchangeability.

IV. Considerations for Developing Presentations for Interchangeable Products

AAM and the Council welcome more specific guidance from FDA on considerations related to the drug delivery system to support interchangeability. A comparative risk analysis is a useful and welcome tool to assess any potential design differences between the proposed product and the RP and can inform the approach to human factors testing, including validation studies. However, we have fundamental concerns over the proposed comparative use human factors studies contained within the draft guidance.

By their nature, human factors studies are non-quantitative studies, conducted via simulated use to observe and assess the potential for critical errors. Critical errors are those that may affect safe and effective use of the product. With that in mind, human factors studies are designed to serve a qualitative purpose – to identify and evaluate the potential impact of any such errors – and not a quantitative one, such as establishing an error rate. Further, root cause analysis is used to analyze the underlying reason(s) for any observed critical error, to support an overall assessment of the risks of the product and facilitate design changes to enhance safety and effectiveness. In all of this, it is the nature and criticality of an error and its potential impact on safe and effective use that is paramount, such that a critical error that occurs only once may be more significant than multiple non-critical errors, i.e., errors that have no implication on safe and effective use. Additionally, using human factors studies to compare error rates between a proposed and reference product serves only to compound the inappropriateness of relying on such studies for quantitative data in the first instance. Among other things, the errors associated with the reference product, if any, may not be the same as those seen with the intended interchangeable product, which can affect the overall assessment of risk related to a given device.

For these reasons, we encourage FDA to reconsider the recommendation to use comparative human factor studies to evaluate the interchangeability of two presentations. Human factors studies can be an important component of device design and development, but not by comparing error rates between products. For the purpose of evaluating interchangeability, human factors studies should be conducted with the proposed product, include RP users among the study population and designed to provide qualitative data relevant to assessing any differences in presentation relevant to the interchangeability determination.

V. Post-Approval Manufacturing Changes

In the Federal Register notice announcing the availability of the Draft Guidance, FDA requests comments on whether there are considerations in addition to comparability assessments that FDA should consider in regulating interchangeable biological products. In our view, once a biological product is licensed by FDA – whether licensed as a biosimilar, interchangeable biological product, or full Biologics License Application – post-marketing manufacturing changes should be subject only to comparability testing. This is because, upon licensure, FDA and the sponsor should have a sophisticated understanding of the product and the factors to consider in assessing

comparability. In this respect, biosimilar and interchangeable biological products will be on par with the RP and should be treated in a similar manner with respect to post-marketing manufacturing changes. If the manufacturer of an RP demonstrates comparability under current FDA policies, the pre- and post-change products are presumed to be interchangeable in terms of safety and effectiveness in all indications. The same rule should apply to interchangeable biological products.

We are also concerned that if FDA imposes more and unnecessary requirements on interchangeable biological products, it will create disincentives for sponsors to make manufacturing improvements that could result in cost savings. It also could open the door to evergreening strategies by RP manufacturers to impede competition from interchangeable biological products based upon migrating manufacturing changes. A consistent approach to post-marketing manufacturing between RPs and interchangeable biological products will mitigate these risks.

VI. New Indications

In its Federal Register notice, FDA requests input on how sponsors and the Agency should handle situations where the RP is approved for an additional indication after licensure of an interchangeable biological product. As discussed previously, we oppose FDA's expectation that a sponsor should demonstrate interchangeability for *all* indications for which the RP is licensed, even if the sponsor is not seeking licensure for all such indications. Accordingly, unless the sponsor of the interchangeable product is seeking licensure for the newly-approved indication, we do not believe any action would be appropriate or necessary.

However, with regard to conditions of use that are licensed for the reference product after an interchangeable biologic product has been licensed, the Agency should assume that a prior interchangeability determination applies to a newly-approved indication absent significant scientific questions regarding that prior determination. In other words, the previous interchangeability determination should be extrapolated to the newly approved indication(s). It is worth noting that this position was initially advocated by AbbVie. Indeed, in its prior Citizen Petition on interchangeability, AbbVie stated that 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."²² We agree. Relatedly, we urge FDA to clarify that an interchangeability determination for a biosimilar can be leveraged broadly and, for instance, applied to cases where the biosimilar sponsor is seeking licensure for a new alternate presentation of the RP. Otherwise RPs manufacturers may pursue evergreening strategies by making small changes to its product, such as presentation or concentration, and frustrate the purpose of the BPCIA by preventing competition.

In the event the sponsor of a reference product obtains a new indication that is not covered by pediatric or orphan exclusivity, AAM and the Council propose that sponsors of interchangeable biologics should be permitted to submit a request to the agency to obtain the new indication by applying the concept of extrapolation. The regulatory pathway could be a CBE-0, although we appreciate that other regulatory pathways could be considered. Irrespective of the regulatory pathway, it is important that the Agency act expeditiously on the request. The Agency already follows a

²² AbbVie Petition at 15.

similar approach for follow-on biologics that will be deemed to be biosimilars in 2020, and other biologic products currently regulated as drugs.

VII. Conclusion

In sum, AAM and the Council appreciate FDA's efforts to make interchangeable biological products a reality by issuing its long-awaited Draft Guidance. We believe the Draft Guidance is an important step forward, and we support many of the concepts outlined in the Draft Guidance. As noted above, we also are concerned that several of the proposals are unduly burdensome and are thus respectfully requesting that FDA make some revisions to the Draft Guidance before finalizing it. We believe these revisions are necessary to ensure that Draft Guidance is as consistent as possible with the intent of the BPCIA to create a streamlined licensure process that encourages and facilitates increased access to safe, effective and affordable interchangeable biological products.

We thank you for your consideration of these comments. If you have any questions, please do not hesitate to contact the undersigned.

Sincerely,

A handwritten signature in black ink, appearing to read "D.R. Gaugh". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

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



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