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**By Electronic Submission**

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**Re: Docket No. FDA–2017–D–0154: Considerations in Demonstrating Interchangeability with a Reference Product; Draft Guidance for Industry; Availability**

Dear Sir or Madam:

AbbVie, Inc. (AbbVie) is pleased to offer comments on the agency's draft guidance *Considerations in Demonstrating Interchangeability with a Reference Product*.[1] AbbVie has deep expertise in the discovery, development, and manufacture of innovative biologic therapies to treat serious diseases. Since enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010, AbbVie has engaged with FDA on many of the scientific and legal issues presented by the new law, consistently emphasizing the need to prioritize patient safety and informed treatment decisions.[2] These same concerns animate our comments here. We appreciate FDA's consideration of them.

Biologics are far more complex than small molecule drugs and, therefore, biosimilars of reference biologics cannot be regulated like generic copies of reference listed drugs. Biosimilars are not identical to their reference products, and the differences between them, even very small differences, can cause harmful immune responses when patients are switched or alternated between the products. Congress recognized this when enacting the statutory approval pathways for biosimilars and interchangeable biologics and established interchangeability as a different and higher standard than biosimilarity. In entrusting FDA with the implementation of these pathways, Congress sought to ensure heightened protection for "any given patient" who could face a change in therapy without the intervention of his or her physician. AbbVie believes the draft guidance falls short of this congressional intent.

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[1] FDA, Draft Guidance for Industry: Considerations in Demonstrating Interchangeability with a Reference Product (Jan. 2017) [hereinafter Draft Guidance].

[2] *E.g.*, AbbVie, Citizen Petition on Interchangeability, Docket No. FDA–2015–P–4935 (Dec. 16, 2015) [hereinafter AbbVie Interchangeability CP]; AbbVie, Comments on Draft Guidance for Industry: Labeling for Biosimilar Products, Docket No. FDA–2016–D–0643 (Aug. 2, 2016); AbbVie, Citizen Petition on Biosimilar Labeling, Docket No. FDA–2015–P–2000 (June 2, 2015).

When FDA approves one biological product as "biosimilar" to another, the agency must find that the two products are "highly similar" with "no clinically meaningful differences."[3] That finding does not rule out the possibility that differences between the two products may result in varying clinical effects in some patients. In contrast, when FDA determines that a biosimilar can be substituted for the reference product without the intervention of the treating physician—that is, finds the biosimilar "interchangeable"—the agency must, by statute and in the interest of public health, rule out even the most minor differences in clinical performance. FDA must determine that interchangeable biological products will do more than perform similarly; it must find that "any given patient" can expect the "*same* clinical result" regardless of the product dispensed and regardless of repeated switching between the products.[4] Moving from one product to another can prime the immune system to recognize subtle differences in structure and trigger or increase the overall immune response to the medicine, which can lead to differences in safety and effectiveness.[5] This immunogenicity concern is paramount for patients—particularly patients suffering from serious, chronic diseases who may have achieved disease control with a reference product—and by statute the concern must be resolved before a biosimilar is deemed interchangeable.

Ruling out any differences in clinical performance between two biologics that may arise in only a small subset of patients is far more challenging than showing that two products are biosimilar. Demonstrating interchangeability will require more rigorous study designs, more stringent comparisons of endpoints, patient-level as opposed to population-level statistical analysis, and robust postmarketing data. The interchangeability assessment is much more demanding than the biosimilarity assessment, but that is what the statute and public health require.

Our comments address five issues that FDA should correct in final interchangeability guidance: (I) FDA should give explicit, independent meaning to the separate provisions of the statutory interchangeability standard to ensure the safe use of interchangeable biologics as Congress intended; (II) FDA should prescribe more robust interchangeability study endpoints and statistical methods than those recommended for use in the draft guidance; (III) FDA should seek robust postmarketing data to support interchangeability determinations for most biological products; (IV) FDA should recommend human factors data assessing the impact of *switching* between the reference and proposed interchangeable biological product presentations; and (V) FDA should require labeling to ensure safe use of interchangeable biological products when multiple biosimilar products have been found interchangeable with the same reference product.

## I. Each provision of the statutory interchangeability standard must be given independent meaning in order to ensure the safe use of interchangeable biological products.

The Public Health Service Act (PHSA) requires FDA to make three discrete findings before licensing a biological product as interchangeable with its reference product:

[3] PHSA § 351(i)(2).

[4] *Id.* § 351(k)(4)(A)(ii) (emphasis added).

[5] Draft Guidance, lines 586–88.

- First, the agency must find that the proposed interchangeable biological product is biosimilar to the reference product—that is, that the product is "highly similar" to and has "no clinically meaningful differences" from its reference product.[6]

- Second, the agency must determine that the proposed interchangeable biological product "can be expected to produce the same clinical result as the reference product in any given patient"[7]—that is, whenever a pharmacist substitutes the interchangeable biological product for the prescribed reference product the patient can be expected to experience the same clinical effects as he or she would if given the reference product.

- Third, if the proposed interchangeable biological product is to be "administered more than once to an individual," FDA must determine that the risk in terms of safety or diminished efficacy of alternating or switching between the product and its reference product is not greater than the risk of remaining on the reference product[8]—that is, the agency must find that alternating or switching between the products will not cause an immune reaction or therapy disruption that would make the therapy less effective or less safe.

As a matter of statutory interpretation, each of the three distinct findings set forth in the law must be construed "so that no part will be inoperative or superfluous, void or insignificant."[9] In the draft guidance, FDA fails to honor this principle of statutory interpretation. In so doing, the agency significantly weakens the interchangeability standard, conflates the interchangeability standard with the biosimilarity standard, and lessens the protections afforded to patients who may face changes in therapy—potentially multiple times—without the intervention of their prescribers.

To begin with, FDA reads the "expected to produce the same clinical result" required finding out of the statute. The draft guidance states that the data and information necessary to satisfy the "same clinical result" requirement "may include, but need not be limited to, an evaluation of data and information generated to support a demonstration of a biological product's biosimilarity."[10] This statement implies that, in some cases, the evidence submitted to show interchangeability may be *limited* to the data derived from studies designed to show biosimilarity only, i.e., that "the same clinical result in any given patient" standard in PHSA § 351(k)(4)(A)(ii) requires nothing more than what was required to demonstrate biosimilarity as set out in (k)(4)(A)(i). This approach cannot be squared with basic principles of statutory interpretation. The finding that two products "can be expected to produce the same clinical result in any given patient" must mean something different from finding "no clinically meaningful differences" between the two products.[11] As a matter of law and public health—as set out

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[6] PHSA §§ 351(i)(2) & (k)(4)(A)(i).

[7] *Id.* § 351(k)(4)(A)(ii).

[8] *Id.* § 351(k)(4)(B).

[9] *Hibbs v. Winn*, 542 U.S. 88, 101 (2004) (quoting 2A N. Singer, STATUTES AND STATUTORY CONSTRUCTION § 46.06, pp. 181–86 (6th rev. ed. 2000)).

[10] Draft Guidance, lines 79–83.

[11] *See Sosa v. Alvarez–Machain*, 542 U.S. 692, 712 n.9 (2004) ("[W]hen the legislature uses certain language in one part of the statute and different language in another, the court assumes different meanings were intended.")

in the introduction above—the data, information, and conclusions used to demonstrate biosimilarity are insufficient; additional data and information are necessary.

Moreover, the draft guidance also diminishes the "same clinical result in any given patient" standard by suggesting that this standard could be met by any study designed and conducted to satisfy the "alternating or switching" statutory standard. Specifically, FDA writes that satisfying the "alternating or switching" requirement will generally require "a switching study or studies."[12] Elsewhere the draft guidance states that the data and information to support a showing under the "same clinical result in any given patient" requirement "will likely not involve additional clinical studies other than those necessary to support other elements of demonstrating interchangeability."[13] The problem with this statement is that it raises the concern that the agency may not be giving the "same clinical result in any given patient" provision independent meaning. Any study intended to satisfy both provisions must collect data and information relevant to the robust standards *in each*. Put another way, any switching study or studies that would alone satisfy the interchangeability standard must evaluate the risks of "alternating or switching" *and also* address the distinct "same clinical result in any given patient" statutory standard. If a study is indeed intended to help conclude that both of these robust standards are met, it should have the scientific rigor outlined in Section II.

## II. The endpoints and statistical methods FDA recommends for use in assessing interchangeability are insufficient to ensure patient safety.

As pointed out above, FDA must give each provision of the statutory interchangeability standard independent meaning in order to ensure the safe use of interchangeable biological products, as Congress intended. The approach described in the draft guidance—a switching study with pharmacokinetic (PK) and, if available, pharmacodynamic (PD) primary endpoints, evaluated under broad, population-level acceptance criteria[14]—fails to satisfy this statutory mandate and is not sufficient to ensure patient safety.

### *A. To comply with the "same clinical result" and "alternating or switching" requirements, the guidance should call for a statistically robust analysis of efficacy endpoints and a comprehensive assessment of potential immunogenicity risks associated with alternating or switching.*

The draft guidance requests clinical data to support interchangeability in the form of a switching study that would compare the bioavailability or PK of the two study arms after the last switch in the study.[15] The guidance mentions the potential use of safety, immunogenicity, and efficacy or PD

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(quoting 2A N. Singer, STATUTES AND STATUTORY CONSTRUCTION § 46:06, p. 194 (6th rev. ed. 2000)); *see also Nat'l Fed'n of Indep. Bus. v. Sebelius*, 132 S. Ct. 2566, 2583 (2012) ("Where Congress uses certain language in one part of a statute and different language in another, it is generally presumed that Congress acts intentionally.").

[12] Draft Guidance, line 127.

[13] *Id.*, lines 113–16.

[14] *Id.*, lines 358–60.

[15] FDA asks for trough PK sampling after each switch only "to ensure that steady state is attained." *Id*., lines 429–30.

endpoints,[16] but minimizes those measurements, considering them secondary endpoints[17] to be sampled as justified by the sponsor[18] and analyzed descriptively.[19] AbbVie is concerned about the emphasis on PK endpoints in the proposed switching study because they can neither sufficiently assess and resolve immunogenicity risk relevant to the "alternating or switching" standard, nor satisfy the "same clinical result in any given patient" statutory standard. PK measurements alone cannot establish that two biologics are interchangeable.

First, PK endpoints will not identify all differences in clinical efficacy between a proposed interchangeable biological product and its reference product. Modifying some structural attributes of biological products can alter molecule function and efficacy independent of an effect, if any, on PK, including bioavailability. For example, there is a significant body of scientific literature setting out the relationship between monoclonal antibody (mAb) glycosylation patterns and the ability of the protein to bind to relevant immune cells via the fragment crystallized (Fc) region of the molecule.[20] Fc binding—and thus glycosylation—can impact the ability of mAbs to, among other things, destroy cells associated with inflammatory response (antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC))[21] or attract immune-regulating cells to inflamed tissue (induction of regulatory macrophages).[22] These Fc-dependent functions can play critical roles in the functioning and efficacy of mAbs.[23] The importance of glycosylation to efficacy is independent of the impact, if any, that the sugars would have on molecule clearance. In fact, for most glycans, a relationship to PK has not

[16] *Id.*, lines 377–78.

[17] *Id.*, lines 444–45.

[18] *Id.*, line 431.

[19] *Id.,* lines 444–45.

[20] *See, e.g.,* Jefferis R. *Glycosylation as a strategy to improve antibody-based therapeutics*. Nat Rev Drug Discov. 8:226-34 (2009); Lingg N et al. *The sweet tooth of biopharmaceuticals: importance of recombinant protein glycosylation analysis.* Biotechnol J. 7(12):1462–72 (2012).

[21] Jefferis (2009); Lingg et al. (2012); *see also* Pace D et al. *Characterizing the effect of multiple Fc glycan attributes on the effector functions and FcγRIIIa receptor binding activity of an IgG1 antibody*. Biotechnol Prog. 32(5):1181–92 (2016) (correlating the effect of the degree of glycosylation for various carbohydrates on mAb Fc binding and resulting cytotoxicities).

[22] Vos A et al. *Regulatory macrophages induced by infliximab are involved in healing in vivo and in vitro*. Inflamm Bowel Dis. 18(3):401–08 (2012).

[23] *See id*.; Jefferis (2009) ("[E]xtensive investigation of the mechanism(s) by which rituximab can kill cD20-positive lymphocytes *in vitro* and *in vivo* has established that recruitment and activation of FcγRIIIa-expressing cells—for example, natural killer (NK) cells—is a dominant pathway."); FDA, *FDA Briefing Document, Arthritis Advisory Committee Meeting, February 09, 2016, BLA 125544, CT–P13, A Proposed Biosimilar to Remicade (infliximab) Celltrion*, at 15–16 ("Finally, there are some potential functions dependent on the Fragment crystallizable region (Fc) part of the antibody that may be important. These include antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) of lysis of mTNF+ inflammatory T-cells or other cells associated with particular disease states. The relative importance of merely sequestering sTNF vs. eliciting other effector functions on mTNF+ cells may vary between disease states.").

been established.[24] Biosimilar sponsors have also recognized that glycosylation differences are related to molecule function and efficacy independent of PK.[25]

Because PK measures alone cannot capture all potential functional differences between the reference and proposed interchangeable products, a comparative PK assessment cannot ensure that the "same clinical result" can be expected in "any given patient." Therefore, a robust comparative efficacy assessment is needed to obtain that information. But the comparative efficacy assessments specifically designed and performed to support the biosimilarity showing are insufficient for this purpose. Those studies are designed to satisfy the biosimilarity standard and, in particular, the finding of "no clinically meaningful differences" between the products.[26] And therefore, by design, they are inadequate to satisfy the separate and higher standard of "expected to produce the same clinical result in any given patient." For instance, the equivalence margins in biosimilarity studies generally are selected to ensure a preservation of treatment effect of the reference product over placebo of between 50 and 60 percent.[27] But a study that gives confidence that 60 percent of patients who would achieve a minimal response to the reference product will also achieve a minimal response to the biosimilar inspires no

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[24] *See* Liu L et al. *Pharmacokinetics of IgG1 monoclonal antibodies produced in humanized Pichia pastoris with specific glycoforms: a comparative study with CHO produced materials*. Biologicals. 39:205–10 (2011) (stating that "[t]he impact of such changes [in glycosylation] to Fc effector functions on mAb PK is controversial" and describing conflicting assessments and a lack of correlation between glycosylation and pharmacokinetics in the researchers' own experiments); Liu L. *Antibody glycosylation and its impact on the pharmacokinetics and pharmacodynamics of monoclonal antibodies and Fc-fusion proteins*. J Pharm Sci. 104:1866–84 (2015) (stating that "glycan removal do[es] not appear to provide a meaningful impact on the PK properties of IgG *in vivo* . . . [and] the observations of similar PK properties between glycosylated and nonglycosylated IgG suggest that the primary factor determining the PK of an IgG (i.e., FcRn-mediated recycling) is not impaired by glycan removal" and noting the way in which select carbohydrates (for example sialic acid) might influence PK).

[25] For example, when Amgen compared the glycosylation of its adalimumab biosimilar and Humira® (the reference product), it characterized the clinical relevance of various glycans—identifying some as relevant to PK and others as relevant to function and efficacy only. Amgen Inc., *Background Information for the Arthritis Advisory Committee 12 July 2016, Biologics License Application for ABP 501*, at 45 (Jun. 9, 2016) [hereinafter *Amgen Briefing Document*].

[26] *See* FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 18 (2015) [hereinafter Scientific Considerations Guidance] ("As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there is residual uncertainty about whether there are *clinically meaningful differences* between the proposed product and the reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment." (emphasis added)). *See also* FDA, Drug Approval Package: Amjevita (adalimumab-atto), Nikolay P. Nikolov, M.D., Cross Discipline Team Leader Review, at 26 (Sept. 23, 2016) ("While ideally the similarity margin would be selected based on a consensus of what magnitude of difference for the endpoint *is not clinically meaningful*, in practice sample sizes may be constrained by feasibility concerns." (emphasis added)).

[27] FDA, Drug Approval Package: Erelzi, Statistical Reviews, Review of Kathleen Fritsch, Ph.D. at 27 (Apr. 28, 2016) ("The applicant justified the choice of an 18% similarity margin noting that 18% *maintains 60% of the observed treatment effects relative to placebo* (45-46%) reported in Leonardi (2003) and Papp (2005)." (emphasis added)); FDA, Drug Approval Package: Inflectra, (infliximab-dyyb) for Injection, Statistical Reviews, Review of Gregory Levin, Ph.D. at 17 (May 4, 2015) ("The lower bound of the proposed similarity margin (-12%) also corresponds to the retention of approximately 50% of conservative estimates of treatment effect sizes relative to placebo for infliximab (Table 2).").

confidence that the biosimilar is expected to produce the "*same* clinical result in *any* given patient."[28] Further, asking sponsors to reanalyze unblinded data from biosimilarity studies using a post hoc, more stringent equivalence margin—in order to meet the more stringent "same clinical result" standard—would introduce potentially insurmountable concerns of bias.[29]

Second, PK endpoints alone cannot reliably detect all differences in immunogenicity. As the draft guidance notes, alternating or switching may cause an immunogenic reaction that would not arise when using the reference product or biosimilar alone.[30] Immunogenic reactions can have both efficacy and safety implications that occur independent of any effect on PK.[31] Therefore, understanding the

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[28] Indeed one statistical expert on the FDA advisory committee considering the CT–P13 and ABP 501 biosimilars expressed concern on multiple occasions about whether an equivalence margin designed to preserve 50 percent of treatment effect would be sufficiently rigorous to satisfy even the "no clinically meaningful differences" standard. *See* FDA, AAC Meeting, Consideration of Amgen's ABP 501, Transcript, at 359:11–19 (July 12, 2016) ("I did want to make a comment, just a more general comment, really, for the FDA in general, that I'm not really sure I'm comfortable with preserving 50 percent of the benefit as being equivalent to saying something is highly similar. It's similar. It's better than nothing; a lot better than nothing. But I'm a little uncomfortable with that.") (Comment of Erica Brittain, Ph.D., Deputy Branch Chief and Mathematical Statistician, Biostatistics Research Branch, NIAID); FDA, Arthritis Advisory Committee (AAC) Meeting, Consideration of Celltrion CT-P13, Transcript, at 225:20–226:6, 368:6–36915 (Feb. 9, 2016) (Comment of Erica Brittain, Ph.D., Deputy Branch Chief and Mathematical Statistician, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases (NIAID)).

[29] *See, e.g.*, Hahn S. *Understanding noninferiority trials*. Korean J Pediatr. 55(11):403-07 (2012) ("Testing noninferiority based on an ad hoc determination of a noninferiority margin after a trial is complete would not be acceptable due to bias."); Committee for Proprietary Medical Products. *Points to consider on switching between superiority and non–inferiority*. Br J Clin Pharmacol. 52(3):223–28 (2001) ("A conclusion of equivalence or noninferiority clearly depends upon the value of Δ chosen as the maximum acceptable difference. It is always possible to choose a value of Δ which leads to a conclusion of equivalence or noninferiority if it is chosen after the data have been inspected. Since the choice of Δ is generally a difficult one, there is ample room for bias here, however, well intentioned the researcher may be.").

[30] Draft Guidance, lines 343–48 ("If an apparent difference in immune response or adverse events is noticed between the switching and non-switching arms of the study . . . , it would raise concerns as to whether the proposed interchangeable product is interchangeable, regardless of whether the proposed interchangeable product or the reference product *or the switching of the two products actually caused the event*." (emphasis added)); *see also* Dan Stanton, *Senate committee to US FDA: where are the biosimilar guidelines?* BioPharma-Reporter.com (Sept. 18, 2015), http://www.biopharma-reporter.com/Markets-Regulations/Senate-Committee-to-US-FDA-Where-are-the-biosimilar-guidelines (quoting Janet Woodcock, M.D., Director, CDER, as stating at a September 2015 Senate Health Subcommittee hearing that "What the concern has been is that this [continued switching] would raise that immunity—sort of provide a booster effect and cause untoward effects.").

[31] Shankar G et al. *Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides—harmonized terminology and tactical recommendations.* AAPS J. 16(4):658–73 (2014) ("[S]afety issues may not necessarily correlate with any effects on PK or efficacy"). *See also* FDA, Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products 3–6, 33–34 (Aug. 2014) [hereinafter Immunogenicity Guidance]. The Immunogenicity Guidance identifies the potential for immune responses to affect PK, but goes on to describe mechanisms by which immune responses can affect safety and efficacy independent of any impact on PK. *See, e.g., id.*, at 33 ("Neutralizing antibodies bind to distinct functional domains of the therapeutic protein product and preclude their activity. . . . In rare circumstances, neutralizing antibodies may act as a *carrier* and enhance the half-life of the product and prolong its therapeutic effect. As discussed in Section III of this guidance, non-neutralizing antibodies bind to areas of the therapeutic protein product other than specific functional domains and may exhibit

effect of immunogenicity means examining the formation of an immune response and its potential impact on efficacy and safety, not simply measuring exposure. With this understanding, FDA has taken the position—in other contexts—that immunogenicity assessments for therapeutic protein products should examine more than PK.[32] The agency has further noted that "[p]harmacodynamic biomarkers may be useful in the assessment of antibody-mediated interference with product activity, although correlation with clinical response is usually necessary to determine clinical relevance."[33] Even in FDA guidance on demonstrating biosimilarity, the agency recommends that comparative immunogenicity studies assess antibody incidence, titer, and neutralizing activity—not simply PK.[34]

The draft guidance's limited discussion of immunogenicity is therefore very hard to understand. The draft guidance makes only passing reference to issues around the sampling for immunogenicity and PD measures.[35] It does not highlight the need for a comprehensive assessment of immunogenic responses to alternating or switching. It does not address how the concerns and issues identified in FDA's existing immunogenicity guidance should be considered and resolved in the interchangeability exercise.[36] And, most concerning, it does not address whether and how sponsors should resolve immunogenicity signals that were detected during the biosimilarity assessment.

This last omission is particularly concerning, given the fact that immunogenicity questions have arisen within the context of at least some of the biosimilarity assessments that have become public. For example, in the course of approving the infliximab biosimilar, Flixabi, in the EU, 14 of the 37 members of the Committee for Medicinal Products for Human Use (CHMP) dissented formally from the CHMP's

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a range of effects on safety and efficacy—enhanced or delayed clearance of the therapeutic protein product, which may prompt consideration of dosing changes, induction of anaphylaxis, diminished efficacy of the product by causing uptake of the therapeutic protein product into FcR-expressing cells rather than target cells, and facilitation of epitope spreading, allowing the emergence of neutralizing antibodies.").

[32] Pursuant to its Immunogenicity Guidance, for chronic use biologics FDA routinely requests a year-long immunogenicity assessment, Immunogenicity Guidance, at 34, with frequent sampling for anti-drug antibodies—particularly at initiation and early use of a chronic use product and upon observation of adverse events, *id.,* at 6–7. According to agency guidance, "[r]epeat sampling should generally occur over periods of sufficient duration to determine whether these [immunogenicity] responses are persistent, neutralizing, and associated with clinical sequelae." *Id.,* at 7. FDA asks sponsors to investigate immunogenicity more extensively in those patients who "lose efficacy, regardless of the duration of the treatment course" in order to "determine whether the loss of efficacy is antibody mediated." *Id*., at 34.

[33] *Id.,* at 3.

[34] Scientific Considerations Guidance, at 17. Although comparative immunogenicity of the reference product and biosimilar is assessed in establishing biosimilarity, the interchangeability exercise needs to provide a comprehensive assessment of the *new* source of potential immunogenicity stemming from repeated switching between the reference and proposed interchangeable products.

[35] *See* Draft Guidance, lines 427–31.

[36] *See* Scientific Considerations Guidance, at 16–18. In that guidance, FDA discusses over the course of two pages key immunogenicity concerns to be addressed in the biosimilarity exercise and the considerations for biosimilar sponsors developing a clinical program to assess immunogenicity risks.

positive opinion of the product due to immunogenicity issues that emerged in clinical testing.[37] The clinical pharmacology and comparative efficacy studies submitted by the product sponsor showed an increased incidence of anti-drug antibody (ADA) formation for patients receiving Flixabi as compared to patients receiving the reference product, Remicade.[38] These CHMP members did not believe the differences could be ignored as chance findings and noted that ADA formation may be associated with decreased efficacy.[39] The European Commission authorized Flixabi on May 26, 2016 determining that these immunogenicity signals did not preclude a finding of biosimilarity. It is our understanding that Renflexis, licensed by FDA on April 21, 2017, is the same product.[40] Nor is this the first biosimilar FDA has approved notwithstanding potential immunogenicity issues that may be relevant to interchangeability.[41] As a matter of statute and patient safety, any residual uncertainty regarding immunogenicity relevant to the interchangeability assessment that is identified during the biosimilarity exercise—particularly how immunogenicity responses can be exacerbated by alternating or switching between the two products—must be resolved in the course of an interchangeability assessment. This cannot be done with PK endpoints alone.

In sum, FDA should revise the draft guidance to recommend that switching studies to demonstrate interchangeability provide a comparison of efficacy under more stringent margins than

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[37] European Medicines Agency (EMA), CHMP, CHMP Assessment Report for Flixabi, at 85 (Apr. 1, 2016) ("The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of a marketing authorisation of Flixabi as a biosimilar to Remicade and in the indications licensed to Remicade.").

[38] *Id*. ("However an increased [ADA] incidence was observed both in the Phase 1 and Phase 3 studies . . . .").

[39] *Id.* ("Flixabi appears to be associated with a higher incidence of ADA than the originator, Remicade. It is acknowledged that it cannot be excluded that the observed difference was a chance finding or a finding associated with limitations in the immunogenicity assays that were used. . . . It is not possible with reasonable certainty to exclude that the estimated reduction in efficacy of Flixabi was the result of the higher incidence of ADA. In this regard, it is noteworthy that the Phase 3 study showed that the efficacy, regardless of treatment group, was significantly lower in ADA positive patients than in ADA negative patients.").

[40] The FDA clinical review of the Renflexis application noted differences in immunogenicity response between EU Remicade and Renflexis in the same data sets that were considered by the EMA. *See* FDA, Drug Approval Package: Renflexis, Juwaria Waheed, M.D., Clinical Review, at 81 (Jan. 19, 2017) ("As noted above, small numerical differences in ADA formation were seen between SB2 [Renflexis and] EU-Remicade in Study SB2-RA and between SB2, and US-Remicade, and EU-Remicade [in the PK study, SB2-NHV]."). FDA had access to data from the 24-week extension of study SB2-RA, comparing patients switched from EU-Remicade to Renflexis to patients remaining on either Renflexis or EU-Remicade. Per FDA, those data showed that "similar proportions of patients tested positive for ADA in all three treatment groups," and that "ADA rates did not increase differentially between patients who underwent a single transition from EU-Remicade to SB2 [Renflexis] as compared with those who continued EU-Remicade or SB2." *Id.,* at 79. While the data from the study extension were presumably helpful to FDA in evaluating immunogenicity for the purposes of biosimilarity, the extension data do not eliminate the differences in immunogenicity rates that were observed nor are these data sufficient to address the statutory standard for interchangeability. See *infra* note 64.

[41] In Amgen's studies supporting approval of its biosimilar adalimumab, Amjevita, subjects switched from the reference product to the biosimilar had a higher incidence of neutralizing and binding antidrug antibodies than subjects who remained on either alone. *Amgen Briefing Document*, at 107–08 (Figure 47). This difference in ADA incidence became an issue of discussion at the FDA AAC meeting considering ABP 501. *See* FDA, AAC Meeting, Transcript, at 247:4–251:20 (July 12, 2016) (memorializing, in particular, questions from Panel Member Jeremy Adler, M.D., M.Sc.).

those used in the biosimilarity exercise[42] and a comprehensive assessment of immunogenicity associated with repeated switching. Sponsors should be asked to make these evaluations *in addition to* assessing PK. It is necessary to assess efficacy endpoints via a study designed to satisfy both the "alternating or switching" and "can be expected to produce the same clinical result" statutory standards. To show that "alternating or switching" will not increase safety risks due to immunogenicity, the sponsor should comprehensively assess immunogenicity, including close monitoring of the incidence, titer, neutralizing activity, and kinetics of antidrug antibody response throughout the switching study.

### *B. To ensure that an interchangeable biological product can be expected to produce the same clinical result as its reference product in "any given patient," the guidance should call for individual-level bioequivalence assessments.*

The draft guidance recommends a population-level or average assessment of bioequivalence (ABE) as part of the proposed switching study.[43] ABE determines whether the average values for PK parameters measured in two groups—one given the test product, the other the reference—are comparable. This statistical technique compares population averages and represents the conventional statistical method employed in bioequivalence testing for generic, small-molecule drugs. It is also the technique that FDA recommends sponsors use in applications establishing biosimilarity. To give meaning to and satisfy the more stringent, statutory "any given patient" standard, and to focus on clinical impact for individual patients, a sponsor seeking an interchangeability designation must assess whether any patient might be expected to react differently to the proposed interchangeable biological product than to the reference product. As a scientific matter, a statistical approach using ABE will not address the heightened interchangeability standard.

If the applicant's product has been found highly similar to the reference product, one would not expect to see stark clinical or PK differences arising in a significant number of patients. But there might nevertheless exist clinical differences in small subsets of patients. Signals from the limited body of biosimilar postmarketing switching data suggest that conclusions from population-level assessments *can* mask clinical impact for small subsets of patients who may not tolerate a switch between a reference product and a biosimilar. For example, researchers following a Danish registry, DANBIO, concluded that—on average—the 802 rheumatology patients on Remicade for an average of 5.9 years switched to the biosimilar Remsima did not experience a statistically significant increase in disease activity. Yet 16% of patients stopped treatment within 12 months of the switch because of loss of efficacy or adverse events.[44] The researchers have warned that these discontinuations *"warrant[] further investigation*

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[42] Validated PD endpoints may also be appropriate for assessing efficacy during the switching study. These endpoints may be more sensitive than traditional efficacy endpoints, allowing for fewer patients and shorter studies. Draft Guidance, lines 364–71. Where validated PD endpoints are available, they should be evaluated statistically, using appropriately rigorous margins, to provide evidence that the product "can be expected to produce the same clinical result in any given patient." PD endpoints that have not been validated are not a reliable proxy for efficacy and have limited utility in assessing interchangeability.

[43] Draft Guidance, lines 433–42.

[44] Glintborg B et al. *A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry*. Ann Rheum Dis. Published Online May 4, 2017 (http://dx.doi.org/10.1136/annrheumdis-2016-210742).

*before such a non-medical switch can be recommended."*[45] Recent analyses of these registry data have shown that the rate of discontinuation for switched patients was slightly, but statistically significantly, higher than the discontinuation rate for a historical control group of patients remaining on Remicade.[46] This small subset of patients who discontinued treatment because of the switch to the biosimilar exist despite the fact that the trial ultimately showed no difference in patient response to the switch at a population level.[47] Other assessments of real-world data have raised similar concerns.[48]

In order to identify whether small groups of patients may not tolerate a switch in therapy, FDA should employ a bioequivalence analysis that takes into account variability in individual patient responses when subjects are alternated between the reference product and the biosimilar. Variability in how subjects respond to a switch in therapy is called subject-by-formulation interaction variability (SxF variability). ABE and other population-level assessments of bioequivalence do *not* account for SxF variability. Even where two products have identical average performance, a significant number of subjects—depending on the degree of SxF variability—might not experience a response within the

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[45] Glintborg B et al. *A nationwide non-medical switch from originator to biosimilar infliximab in patients with inflammatory arthritis. eleven months' clinical outcomes from the Danbio registry [abstract]*. Arthritis Rheumatol. 68:(suppl 10) (2016), http://acrabstracts.org/abstract/a-nationwide-non-medical-switch-from-originator-to-biosimilar-infliximab-in-patients-with-inflammatory-arthritis-eleven-months-clinical-outcomes-from-the-danbio-registry/ (last visited May 16, 2017)

[46] Glintborg (2017) ("Retention rates were slightly lower in the CT-P13 cohort versus the historic INX cohort, with an adjusted absolute risk difference of 3.4%. This difference is not necessarily attributable to CT-P13, but could also represent a 'nocebo-effect', that is, negative expectations towards the drug or residual confounding.")

[47] Importantly, there is no scientific insight into which patients might not do well when switched from the reference to the proposed interchangeable product.

[48] For example, a switching study sponsored by the Norwegian government also indicated that some patient subsets may have experienced disease worsening when switched to the biosimilar. In the NOR-SWITCH study, patients who had switched from the reference biologic Remicade to the biosimilar Remsima were compared with patients remaining on Remicade. The study met its primary endpoints and showed that comparisons of disease-worsening rates—for all disease-states combined—between the switched and maintaining groups fell within prespecified non-inferiority margins. Nevertheless, some patients experienced disease worsening when switched to the biosimilar, and for some indications the percentage of switched patients experiencing disease worsening was notably higher than those remaining on the reference (e.g., 36.5% of switched Crohn's disease patients experienced disease worsening; 21.2% of Crohn's patients remaining on Remicade experienced disease worsening). Jørgensen KK et al. *Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial*. Lancet. Published Online May 11, 2017 (http://dx.doi.org/10.1016/S0140-6736(17)30068-5). ("We caution against emphasising the treatment differences within each disease when interpreting these data. These analyses are prespecified as exploratory subgroup analyses and the study was not powered to show noninferiority for each of the diagnoses separately. With six diagnosis-specific comparisons there is a substantial multiplicity issue, with a relatively high likelihood of at least one false-positive treatment difference. *We did not reach this difference in our results, although the confidence interval for Crohn's disease was close to inferiority of CT-P13.*" (emphasis added)). Although we have expressed concern about the ability of this study to comprehensively address issues associated with switching, *see* Faccin F et al. *The design of clinical trials to support the switching and alternation of biosimilars'.* Expert Opin Biol Ther. 16(12):1445–53 (2016), the possibility that subsets of patients in some conditions may not respond well to a switch is noteworthy.

bioequivalence range.[49] Where SxF variability is significant, scientists caution that average assessments of bioequivalence may fail to properly evaluate the impact of switching therapies.[50]

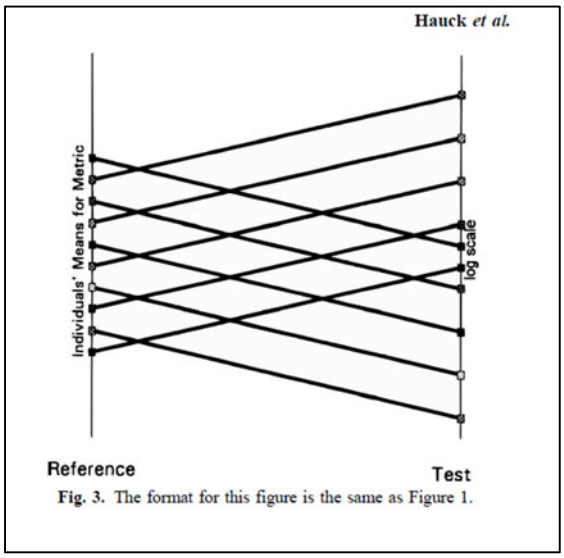

Fig. 3. The format for this figure is the same as Figure 1.

The figure to the left—taken from Hauck et al., *Subject-by-Formulation Interaction in Bioequivalence*—illustrates that significant SxF variability can exist even when the average performance of the two products is the same. The authors explain that each line "connects an individual subject's mean bioavailability data for the test (T) and reference (R) products." In this scenario, the Test product is assumed 50 percent more bioavailable than the Reference product in about half of the subjects, and the Reference is assumed 50 percent more bioavailable than the Test in the remaining subjects. In other words, this is a scenario where subgroups respond differently to the new treatment. The two products would be similar when considered at the population level; that is, the Test would be deemed, on average, bioequivalent to the

[49] Hauck WW et al. *Subject-by-formulation interaction in bioequivalence: conceptual and statistical issues*. Pharm Res. 17(4):375–80 (2000); *see also* Chen ML et al. *An individual bioequivalence criterion: regulatory considerations*. Stat Med. 19(20):2821–42 (2000) ("Even if the overall means are identical, unless $\sigma_D$ [subject-by-formulation variability] = 0, there is some probability that individual ratios outside the interval of 0.80 –1.25 are present. It is estimated that if $\sigma_D$ = 0.136, about 10 per cent of the individuals would have their average ratios outside 0.8–1.25. If $\sigma_D$ = 0.1741, the probability is about 20 per cent. Current FDA thinking [in the generic drug context] is that an interaction is important when 10 per cent or more of individual mean ratios are outside 0.80 –1.25, and a cut–off value of 0.15 has been chosen for $\sigma_D$.").

[50] Bialer M. *Generic products of antiepileptic drugs (AEDs): is it an issue?* Epilepsia. 48(10):1825–32 (2007) ("Generic AEDs with documented average bioequivalence data that were approved by the regulatory authorities as interchangeable (prescribable) represent a valuable choice for patients who are 'naive' to the drug and have not been exposed to any of its formulations. The answer to the question posed in the title of this manuscript is that the crux of the issue with generic AEDs lies in the switchability of epileptic patients who are seizure–free or have achieved complete seizure remission. In light of the fact that currently there is no regulatory consensus on individual bioequivalence criteria, would generic AED products need to have documented individual bioequivalence data in order to be approved as switchable to the brand AEDs?"). *See also*, *e.g.*, Ibarra M et al. *Sex-by-formulation interaction assessed through a bioequivalence study of efavirenz tablets*. Eur. J. Pharm.Sci. 85:106–11 (2016) ("Due to gastrointestinal differences, men and women produced a dissimilar discrimination of EFV [(efavirenz)] oral formulations, introducing a sex-by-formulation interaction in bioequivalence for CMAX. The presence of this interaction could have a major impact on bioequivalence conclusions; therefore its presence should be investigated."); Chen ML. *Fundamentals of bioequivalence*. In Yu L, Li B. FDA Bioequivalence Standards, AAPS Advances in the Pharmaceutical Sciences Series 13. pp. 29–53, at 43 (2014) (describing several situations in which researchers have identified SxF variability that could potentially impact the validity of average bioequivalence determinations).

Reference. But that comparability in average performance misses the significant drop-off in bioavailability for some subjects.[51]

Among the many statutory and regulatory provisions governing FDA product approval and substitution, the "any given patient" phrase in subsection (k)(4)(A)(ii) stands out.[52] To ensure that this phrase is given meaning, the agency should recommend that the sponsor of a proposed interchangeable biological product use a bioequivalence assessment that measures SxF variability and identifies acceptance criteria that would bound that variability within justifiable margins.[53] The agency has identified individual bioequivalence (IBE) as a statistical model suitable for identifying and assessing the impact of SxF variability in some contexts.[54] There exist other statistical bioequivalence assessment options that have been proposed specifically to address SxF variability and support a showing of interchangeability, and these alternatives could also be considered by FDA.[55]

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[51] *See generally* Hauck (2000), at 375–76. The vertical axis is in log scale, so parallel lines correspond to equal percentage changes between the two formulations in the original scale of the bioavailability measure (AUC or Cmax).

[52] With respect to regulatory provisions addressing substitution, compare the language in the BPCIA to the Orange Book, which provides that drug products are considered to be therapeutic equivalents only if they "can be expected to have the same clinical effect and safety profile *when administered to patients under the conditions specified in the labeling*." FDA, Approved Drug Products with Therapeutic Equivalence Evaluations vii (37th ed. 2017) [hereinafter Orange Book] (emphasis added). Subsection (k)(4)(A)(ii) generally tracks the Orange Book standard for therapeutic equivalence, i.e., substitutability, for small molecules. But Congress conspicuously struck the italicized language and added "*in any given patient*." The draft guidance does not reflect the significance of this change in wording.

[53] Scientific distinctions between biosimilars and generic drugs may justify different statistical approaches for measuring equivalence in the context of biologics interchangeability. For instance, as one expert has noted, "[s]everal biologics, especially antibodies, show high inter-individual variation of pharmacokinetic parameters, which is mainly clearance driven. It is now clear that monoclonal antibodies (Mab's) which target cellular antigens have far more complex, non-linear pharmacokinetics, such that the half-life of these drugs can be both dose and time dependent." Baumann A. *Early development of therapeutic biologics—pharmacokinetics.* Curr Drug Metab. 7(1):15–21 (2006). *See also* Xu X, Vugmeyster Y. *Challenges and opportunities in absorption, distribution, metabolism, and excretion studies of therapeutic biologics*. AAPS J. 14(4):781–91 (2012). Immunogenic reaction to a biologic can also play a role in clearance of the medicine. Because immunogenicity responses for some patients might affect bioavailability for those patients, SxF variability takes on greater significance for biologics than for small molecule drugs.

[54] FDA, Guidance for Industry: Statistical Approaches to Establishing Bioequivalence 3 (Jan. 2001) ("The individual BE approach assesses within-subject variability for the T and R products, as well as the subject-by-formulation interaction.").

[55] *See, e.g.*, Li J, Chow SC. *Statistical evaluation of the scaled criterion for drug interchangeability*. J Biopharm Stat. 27(2):282–92 (2016) (proposing an alternative to IBE that also takes into consideration subject-by-formulation variability); Chow SC, Song F, Chen M. *Some thoughts on drug interchangeability*. J Biopharm Stat. 26(1):178–86 (2016); Chen M, Chow SC. *Assessing bioequivalence and drug interchangeability*. J Biopharm Stat. 27(2):272–81 (2017); Chow SC et al. *A new scaled criterion for drug interchangeability*. Chin J Pharm Analysis. 35:844–48 (2015).

## III. Robust postmarketing data will be necessary to establish interchangeability for most biological products.

Robust, on-market data generated after approval as a biosimilar will be crucial for satisfying the heightened interchangeability standard for most products. The draft guidance indicates that extensive and advanced analytic comparisons of the reference product and proposed interchangeable biological product could help to reduce residual uncertainty and lead to a more selective approach to the clinical studies necessary to demonstrate interchangeability.[56] In particular, the draft guidance suggests that a "fingerprint-like characterization" of the proposed interchangeable biological product could eliminate the need for the development of biosimilar postmarketing data prior to an interchangeability designation. This approach threatens to weaken the protections Congress afforded patients via the interchangeability standard.

This section will address the following concerns related to FDA's approach to biosimilar postmarketing data: (1) The FDA "fingerprint-like characterization" criterion is ill-defined and too vague to serve as a basis for agency action; (2) biosimilar postmarketing data are crucial in addressing key immunogenicity and safety concerns that cannot be captured through controlled clinical trials and analytics; and (3) FDA guidance should address important features of a biosimilar postmarketing assessment to support an interchangeability designation.

First, the guidance gives a key role to "fingerprint-like characterization," even though this concept remains vague and undefined. Indeed, three FDA guidance documents have now used the term "fingerprint-like," but to date the agency has said nothing about its meaning except that such an analysis or characterization involves "integrated, multi-parameter" "comprehensive" assessments, that it should cover "a large number of additional product attributes," and that it should be conducted using "orthogonal methods" that are "high[ly]" or "extremely" sensitive.[57] The guidance documents do not provide enough information for meaningful comment from stakeholders on the value of fingerprint-like characterization or its ability to address residual uncertainty as part of a biosimilar development program. As a result, we are concerned about arbitrary application of the standard when actual review decisions are made. We urge the agency to provide concrete details about "fingerprint-like characterization" and to explain how particular analytic assessments could, if at all, address residual immunogenicity concerns within the context of the biosimilarity and interchangeability exercises.

Second, for the purposes of an interchangeability determination, even with the most robust of analytical assessments, postmarketing data are necessary to assess key immunogenicity and safety concerns. As FDA notes, current analytical techniques are limited in their ability to detect differences

[56] Draft Guidance, lines 207–10.

[57] *See* FDA, Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product 5–6 (2016); FDA, Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product 8–9 (2015) [hereinafter Quality Considerations Guidance]; Scientific Considerations Guidance, at 7. We support the notion that one analytic comparison can be more rigorous and demonstrate greater similarity to the reference product than another. We also recognize a role for stricter analytical similarity as a foundation of an interchangeability designation. We *do not*, however, believe that any analytic comparison can eliminate the need for robust clinical and (for most products) on-market assessment of a proposed interchangeable product.

between biological products.[58] Even small analytical differences between a reference product and proposed interchangeable biological product can affect immunogenicity and thus, product safety and effectiveness.[59] Indeed, "immunologic response is highly dependent on the structural differences between the proposed interchangeable biological product and the comparator product used in the switching study[.]"[60] Yet, as FDA has recognized in final guidance, "[s]tructural, functional, and animal data are generally not adequate to predict immunogenicity in humans."[61] Given the residual uncertainty following even the most robust analytic characterization, more is needed to demonstrate interchangeability for complex biologics.

Clinical studies, though critical to the interchangeability exercise, also have limitations. As FDA notes in final guidance, "[r]are, but potentially serious, safety risks (e.g., immunogenicity) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events."[62] Not only may switching trials be too small to detect rare events, but they may be too brief to detect adverse events with long latency periods, which include some immunogenic reactions. Long-term observation of outcomes in treatment-naïve and medically switched patients will provide important information about comparative safety, effectiveness, and immunogenicity not available from inherently shorter-term switching studies in small, homogenous groups. Moreover, signals regarding differences in clinically relevant outcomes might not emerge until a biosimilar is used under real-world conditions. Randomized clinical trials tend to enroll populations that are more homogeneous than real-world populations and may, for instance, exclude subjects of certain ages, subjects having certain co-morbidities, and subjects taking certain concomitant medications.[63] Postmarketing data provide information about use under real-world conditions, which is especially important for interchangeability determinations, given the many patient-related factors that can affect immune reactions.[64]

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[58] Draft Guidance, lines 191–93 ("[C]urrent analytical methodologies may not detect or characterize all relevant structural and functional differences between the reference product and the proposed interchangeable product."); Quality Considerations Guidance, at 6 ("Despite improvements in analytical techniques, current analytical methodology may not be able to detect or characterize all relevant structural and functional differences between the two protein products."); *see also* Scientific Considerations Guidance, at 14, 16.

[59] Draft Guidance, lines 581–95.

[60] *Id.*, lines 588–90.

[61] Scientific Considerations Guidance, at 16.

[62] *Id*., at 22.

[63] *The Clinical Impact of Adverse Event Reporting*. A MEDWATCH Continuing Education Article, at 1, Goldman SA et al., eds. Rockville, MD: Food and Drug Administration (Oct. 1996) ("There are intrinsic limitations to premarketing human clinical trials with respect to their ability to detect adverse events. Short duration, narrow population, narrow set of indications and small size are major factors in this regard, irrespective of the type of medical product being studied."). Indeed, the draft guidance contemplates that a sponsor might perform switching studies in a patient population that is different from that used to support licensure of the reference product or even in healthy volunteers in "some limited situations." Draft Guidance, lines 478–79, 490–91.

[64] Immunogenicity Guidance, at 9–12. For all of the reasons noted in this paragraph, data from any one-time transition (single-switch) in the studies supporting biosimilarity have limited predictive value with respect to interchangeability. These data are gathered to assess major safety risks (e.g., anaphylaxis) associated with use of

Given the limitations of analytic and clinical assessments to address the safety and immunogenicity risks that should be resolved before receiving an interchangeability designation, for most biological products—especially those with immunogenicity potential and a range of approved conditions of use covering multiple therapeutic areas and mechanisms of action—postmarketing data will be an essential component of an interchangeability submission. AbbVie asks FDA to recognize in the final guidance that these data will be necessary for all but the most simple biological products.

Third, to adequately support an interchangeability determination, AbbVie believes postmarketing data should meet three conditions.

- A postmarketing assessment of a proposed interchangeable biological product should draw on data from all conditions of use approved for the reference product. This will help to ensure that conditions of use approved for the biosimilar on the basis of extrapolation are considered under the different and more demanding interchangeability standard.

- The data should primarily be gathered prospectively and should reflect real–world use conditions. Prospectively collected data from real-world conditions—for example, collected as part of a disease or product registry—would be valuable. Collecting data passively or retrospectively has limitations—such as increased risk of bias and challenges in addressing confounding variables—that can undermine results where effects are expected to be relatively small (as would be expected when comparing two products that have already been found to be biosimilar).

- Postmarketing data should derive from use of the U.S.-approved reference product and biosimilar. Use of foreign comparator products would introduce yet another confounding variable to the postmarketing-data analysis. Moreover, the prospect of "bridging" immunogenicity signals from real-world switching using a non-U.S. comparator reference to the U.S.-licensed reference product is fraught with complications.[65] FDA has concluded that a non-U.S. comparator product "would not be appropriate in a switching study."[66] There "may be subtle differences between the U.S.-

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the biosimilar by non-naïve patients. FDA, AAC Meeting, Transcript, at 247:20–248:14, 249:17–19 (July 12, 2016) (statement of Nikolay Nikolov, M.D.); *id.*, at 250:11–21 (statement of Leah Christl, Ph.D.); Scientific Considerations Guidance, at 16–17.

[65] Bridging of clinical data can be challenging even when a sponsor is looking to bridge head-to-head efficacy data from a controlled clinical trial. *See* FDA, Drug Approval Package: Taltz (ixekizumab) Injection, J.P. Phillips, BLA 125521 ixekizumab Mid-Cycle Communication Agenda, at 2 (Aug. 12, 2015) (Administrative Correspondence at 18) (noting sponsor challenges in bridging clinical data using a comparator product from the European Union).

[66] Draft Guidance, lines 578–79. AbbVie agrees. As the agency points out, in clinical studies to support a finding of biosimilarity, the comparator product plays the role of a control against which the proposed biosimilar is evaluated. In clinical studies to support a finding of interchangeability, the comparator product plays a fundamentally different role; the control is "non-switching," and the comparator product is used in the active switching arm. *Id*., lines 572–79. Thus, while non-U.S. comparator products may be appropriate (with bridging data) for biosimilarity studies, they are not appropriate for interchangeability studies. This is consistent with the

licensed reference product and the non-U.S.-licensed comparator product," the draft guidance notes, which creates "uncertainty as to whether the results observed in a switching study using a non-U.S.-licensed comparator product would also be observed if the U.S.-licensed reference product had been used instead."[67] For the same reason, postmarketing data from use of a non-U.S.-licensed comparator product would not be appropriate to support interchangeability. As the draft guidance notes, "establishing interchangeability with a product that patients will not receive in the United States would generally not be appropriate."[68]

## IV. The draft guidance does not address the potential for medication errors associated with *switching* between the presentations of the reference and interchangeable biological products without the intervention of a health care provider.

The draft guidance emphasizes the potential risk of medication errors associated with the use of the proposed interchangeable biological product and provides significant discussion of human factor issues for proposed interchangeable biological product presentations.[69] However, we are concerned that the guidance does not ask sponsors to evaluate how patients familiar with the reference product delivery system will handle the *switch* to a similar presentation without the intervention of the treating physician.

As the agency explained, the key consideration in evaluating whether a biosimilar presentation will allow for an interchangeability determination is whether the sponsor can "demonstrate that the changes [in presentation] do not negatively impact the ability of end users . . . to appropriately use these products when the interchangeable biological product is substituted for the reference product without the intervention of the prescribing health care provider or additional training before use."[70] But the agency proposes only threshold, side-by-side comparisons of product design and human factor studies with naïve patients unfamiliar with the reference product to satisfy this standard. The only way to fully assess whether patients familiar with the use of the reference product delivery system would be confused by a substituted device or presentation and risk medication error would be to "switch" [71]

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fact that the standard for establishing interchangeability is fundamentally different from the standard for establishing biosimilarity.

[67] *Id.*, lines 591–95.

[68] *Id.*, lines 602–05.

[69] For example, we appreciate the agency's recognition that comparative human factor studies for interchangeability may require rigorous margins, *id.*, lines 1023–25, and consequently sample sizes "larger than those described generally in the human factors study literature" because of the unique goals of supporting an interchangeability designation, *id.*, lines 998–1002.

[70] *Id*., lines 681–84.

[71] The agency has noted that a paired design for the sponsor's human factor study could serve as a more efficient alternative to the parallel design. *Id*., lines 987–90. In a paired design, each subject would be exposed to both the reference and proposed interchangeable biological product presentations and would serve as his or her own control. Although a paired design might measure subject experience with the interchangeable biological product presentation after a previous exposure to the reference product presentation, the paired design does not fully

patients familiar with the reference biologic presentation to the proposed interchangeable presentation.[72] Such a "switch" would better evaluate, for example:

- whether familiarity with the reference product device might cause a patient to overlook key design differences that would otherwise be apparent to a device-naïve patient;
- whether design differences between the two devices that might go unnoticed by a device-naïve patient (e.g., color differences, label placement, packaging configuration) would nevertheless create confusion for a patient accustomed to the details of the reference product device; and
- whether patients familiar with the reference product presentation would be more or less likely than a device-naïve patient to carefully review the use instructions included with the proposed interchangeable biological product.

The impact of a switch in delivery device for patients familiar with the reference product presentation would be very difficult to predict with the comparative threshold analyses proposed in draft guidance.[73] As a result, FDA should routinely ask for human factor data assessing the potential for errors experienced by patients familiar with the reference product presentation.

## V. The final guidance should recommend labeling to address situations where multiple biosimilar products are found interchangeable with the same reference product.

The draft guidance does not, but should, address the situation where multiple biosimilars are found interchangeable with the same reference product. The simultaneous marketing of multiple products each of which has been found interchangeable with a particular reference product raises

address risks for patients that have developed familiarity with the reference product presentation as a result of actual biologic use over time.

[72] Moreover, where a proposed interchangeable product seeks approval for fewer than all presentations of the reference product, we have particular concerns about the likelihood that a patient stable on the reference product would be automatically substituted to an unfamiliar presentation (e.g., from an autoinjector approved for the reference product but not the interchangeable biological product to a pre-filled syringe approved for both the reference product and interchangeable biological products). In the draft guidance, FDA articulates similar concerns associated with a sponsor seeking an interchangeability designation using a presentation for which the reference product is not approved. Draft Guidance, lines 653–60. Therefore, where a sponsor is seeking an interchangeability designation with fewer than all of the presentations of the reference product, a sponsor should critically assess—with supporting human factor data—what will happen when a patient is switched to the unfamiliar presentation without the intervention of the prescribing health care provider or additional training.

[73] The Combination Products Coalition (CPC), in comments to a related FDA draft guidance (FDA, Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA (2017)), has also asked FDA to recommend human factor studies that evaluate subjects familiar with the use of the reference listed product device in order to assess the "safety of switching a patient to a generic or biosimilar product." CPC, Comments, Docket No. FDA–2016–D–4412 (Mar. 20, 2017), at 5.

significant patient safety issues. Those safety issues should be addressed, at a minimum, via product labeling.

Different biological products each found interchangeable with a single reference product may have subtle structural differences from each other. Indeed, there may be more structural differences—or different types of structural differences—between two such biological products than exist between either and the reference product. There could also be differences in presentations and devices. It is not scientifically sound to simply assume that two biological products, even if determined interchangeable with the same reference product, can be expected to produce the same clinical result as each other in any given patient or that there is no risk from alternating or switching among them. As a result, two such products cannot be presumed interchangeable with each other.

Section 351(k) of the PHSA authorizes the agency to determine that a biosimilar is interchangeable with its reference product, and it requires data and information evaluating the biosimilar and its reference product for interchangeability.[74] The statutory assessment provides no basis for assuming patient safety in a real-world setting where three-way cross-switching occurs between different biosimilar products, each found interchangeable with the same reference product. As the draft guidance notes, multiple exposures to slightly different proteins can "prime the immune system to recognize subtle differences in structural features between products," triggering or increasing the overall immune response.[75] In a real-world scenario of three-way (or four-way, or more) switching and alternating, the additional and varying structural differences amongst interchangeable biologics may significantly compound the risk of immunogenic or other negative reactions.

Physicians, pharmacists, and patients are nevertheless likely to assume that interchangeable biological products *are* interchangeable with each other. Moreover, reimbursement policies are likely to generate pressure to switch freely between the products. In the small molecule paradigm, a generic drug is understood to be substitutable both with its reference listed drug and with any other generic drug product sharing an "A" rating to the same reference listed drug.[76] As a result, patients are routinely switched between the various substitutable generic equivalents of the particular reference products their physicians have prescribed. In the context of biological products, however, this practice would be medically inappropriate.

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[74] *See, e.g.*, PHSA § 351(k)(3) (authorizing FDA to find a biological product "interchangeable *with the reference product*") (emphasis added); *id.* § 351(k)(4) (specifying the basis for a decision that a biological product is "interchangeable *with the reference product*," which includes that it is "biosimilar *to the reference product*[,]" that it "can expected to produce the same clinical result *as the reference product* in any given patient[,]" and that "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.") (emphases added); *id.* § 351(i)(4) ("The term 'reference product' means the *single* biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).") (emphasis added).

[75] Draft Guidance, lines 586–88.

[76] *See generally* Orange Book at xii-xvii (describing regime where therapeutically equivalent generics of the same reference drug are generally therapeutically equivalent to each other).

FDA should manage this safety issue with labeling. It is imperative that different biosimilar products determined interchangeable with the same reference product not be mistakenly assumed interchangeable with each other. The labeling of an interchangeable biological product should therefore clearly state the scope of the product's interchangeability. In particular, the labeling should state that:

- the product is interchangeable with the reference product and not interchangeable with any other product; and
- once a patient has received a single interchangeable biological product, a different interchangeable biological product should not be substituted for the prescribed reference product without the intervention of a health care provider.[77]

This approach will ensure that any switch between interchangeable biological products of the same reference product will be initiated and monitored by a physician, on the basis of an informed clinical judgment that the switch is safe and warranted in a particular case.

## VI. Conclusion

AbbVie appreciates FDA's consideration of these comments and the agency's efforts to clarify its views on the information necessary to demonstrate interchangeability. This is a topic of critical significance to industry, patients, and the health care community. AbbVie encourages FDA to prioritize patient health and safety in accordance with the statutory framework on interchangeability as the agency revises its draft guidance.[78]

Respectfully submitted,

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[77] *See generally* AbbVie, Comments on Draft Guidance for Industry: Labeling for Biosimilar Products, Docket No. FDA–2016–D–0643 (Aug. 2, 2016), at 4.

[78] On December 16, 2015, AbbVie filed a citizen petition raising significant legal and policy issues associated with FDA's implementation of the statutory interchangeability standard. AbbVie Interchangeability CP. On January 17, 2017, concurrent with the publication of the draft guidance, FDA denied AbbVie's Interchangeability CP by expressing an intent to "consider issues related to interchangeability in the context of the public docket opened for comment on the draft guidance," and encouraging AbbVie to submit comments to the docket. FDA Denial of AbbVie Citizen Petition, Docket No. FDA–2015–P–4935, at 3 (Jan. 17, 2017). Accordingly, we respectfully incorporate by reference the December 2015 AbbVie Interchangeability CP into these comments.