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December 16, 2015

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

CITIZEN PETITION

AbbVie Inc. (AbbVie) respectfully submits this petition under 21 C.F.R. §§ 10.25 and 10.30, and section 351 of the Public Health Service Act (PHSA), as amended by the Biologics Price Competition and Innovation Act of 2009 (BPCIA), and sections 4(e) and 10 of the Administrative Procedure Act (APA).

I. ACTION REQUESTED

AbbVie supports the entry of biosimilars in the United States. We also appreciate the Food and Drug Administration's (FDA's) willingness to consider public input on the critical issues involved in its implementation of its biosimilar authority. We believe, as does FDA, that it will be possible at some point in time for a biosimilar applicant to provide sufficient scientific support to demonstrate that its product is interchangeable with a reference product under the BPCIA.[1] The standards that FDA will use to evaluate interchangeability are of major public health importance because interchangeability determinations will facilitate automatic substitution of biological products, many of which are taken by patients to treat debilitating chronic and potentially life-threatening diseases. Interchangeability determinations must be subject to the highest of standards because an FDA determination that a biological product is interchangeable with another means that any patient prescribed one product (including patients who have been using a product successfully for years) could be switched to another product without the intervention of the patient's healthcare provider.

AbbVie respectfully submits that FDA should, in assessing interchangeability under the BPCIA, ensure that applicants seeking interchangeability determinations meet the "Safety Standards for Determining Interchangeability" set forth in PHSA section 351(k)(4) with respect to *each* condition of use for which the reference product is licensed, regardless of whether the applicant intends to label its product for every such condition of use. AbbVie further requests that FDA clarify that the statutory standards for establishing interchangeability differ in both kind and scope from the standard for establishing biosimilarity. Finally, given the complex

[1] *See* Janet Woodcock, *Biosimilar Implementation: A Progress Report from FDA*, Oral Testimony before the Subcommittee on Primary Health & Retirement Security, Senate Committee on Health, Education, Labor & Pensions (Sept. 17, 2015) (explaining that although scientific issues persist, FDA will likely arrive at approval of an interchangeable biosimilar sometime in the future), *available at* http://1.usa.gov/1Q4bHxR.

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scientific issues raised by interchangeability, AbbVie asks FDA to convene a Part 15 hearing to obtain public input on the topic. Interchangeability raises complex questions that are fundamentally different from those presented by biosimilarity. A public hearing on interchangeability, including the implications of interchangeability determinations in a multi-source product environment where multiple biological products may have been found interchangeable with a single reference product, but not each other, will help to protect patients by ensuring that all viewpoints are heard. The agency should then issue guidance or regulations that address this important public health issue.

II. STATEMENT OF GROUNDS

A. Introduction

The BPCIA amended the PHSA to authorize the "Licensure of Biological Products as Biosimilar or Interchangeable."[2] In early 2015, FDA licensed the first biosimilar biological product, but it has not yet issued an "interchangeability" determination. Indeed, FDA is still "continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product."[3]

In assessing interchangeability, FDA should consider that interchangeability determinations for biological products are, like therapeutic equivalence ratings assigned to generic small molecule drugs, intended to facilitate pharmacy substitution of lower-cost follow-on products for their respective reference products without the intervention of prescribers. Biological products are different, however, from small molecule drugs in two respects relevant to interchangeability determinations.

First, biological products present significant risks of immunogenicity, affecting both patient safety and product efficacy. As FDA stated in 2007:

> To establish that two protein products would be substitutable, the sponsor of a follow-on product would need to demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity. For many follow-on protein products—and in particular, the more complex proteins—there is a

[2] Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Title VII, Subtitle A, § 7002(a)(2), 124 Stat. 119, 805 (2010) (caption of PHSA § 351(k), 42 U.S.C. § 262(k)).

[3] FDA, *Draft Guidance for Industry: Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, 7 (May 2015).

> significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness.[4]

In September 2015, FDA again highlighted the risks of immunogenicity with biological products:

> The question is would [continued switching] cause additional harm because of unexpected immune responses. Because unlike most of our small molecule drugs, the body recognizes these large protein molecules that are biosimilars and often, in some people, will make an immune response. And what the concern has been is that this continued switching could raise that immunity—sort of provide a booster effect and cause untoward effects. . . . Our problem is that the human immune system is capable of detecting tiny variability.[5]

Second, one biological product cannot be the "same as" another. As FDA recently reiterated in final guidance, "[u]nlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product."[6] Thus, while generic and reference listed drugs can be guaranteed (as a scientific matter) to have identical clinical profiles across all indications based on proven structural identity, no such assurances can be presumed to exist between any two biological products, simply because structural identity between such products cannot presently be demonstrated.

These facts, as both a public health and a legal matter, lead to the conclusion that FDA should not find a biosimilar biological product interchangeable with a reference product unless the agency has found the two products interchangeable for *every* condition of use for which the reference product is licensed, regardless of how the interchangeable biological product is labeled. FDA should clarify that the statutory standard for establishing interchangeability differs in both kind and scope from the standard for establishing biosimilarity. FDA should also convene a hearing pursuant to 21 C.F.R. Part 15 to consider the complexities of interchangeability, including the implications of interchangeability decisions in a multi-source product environment where multiple biosimilar biological products may have been found interchangeable with a single reference product, but not each other.

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[4] Janet Woodcock, *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, Written Statement before the Subcommittee on Health, House Committee on Energy & Commerce (May 2, 2007) (May 2007 Woodcock Testimony).

[5] Janet Woodcock, *Biosimilar Implementation: A Progress Report from FDA*, Written Statement before the Subcommittee on Primary Health & Retirement Security, Senate Committee on Health, Education, Labor & Pensions (Sept. 17, 2015).

[6] FDA, *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, 5 (Apr. 2015) (Scientific Considerations Guidance).

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B. Interchangeability Determinations For Biological Products Are Intended To Have The Same Practical Effect As Therapeutic Equivalence Ratings For Small Molecule Drugs.

The real-world effect of an interchangeability determination for a biological product is intended to mirror the real-world effect of a therapeutic equivalence rating for a generic small molecule drug.

FDA developed the concept of therapeutic equivalence ratings in the late 1970s, in response to requests by state governments seeking guidance on how to best encourage the safe substitution of equivalent small molecule drug products.[7] Although state substitution laws have evolved in the forty years since, their goal has always been the same: to ensure that the generic substitute dispensed by a pharmacist is equivalent to the branded product prescribed by the health care practitioner.

For a small molecule drug, an "A" rating denotes "therapeutic equivalence," which has two primary components: pharmaceutical equivalence (same active ingredient, route of administration, dosage form, and strength), and bioequivalence (no significant differences in the rate or extent to which the active ingredient or moiety becomes available at the site of drug action, when administered at the same molar dose under similar conditions).[8] As explained by FDA, "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[9] State pharmacy laws track this conclusion: therapeutically equivalent generic drugs are generally dispensed in lieu of prescribed reference products in all states.

Interchangeability determinations for biological products under the PHSA likewise are intended to guide substitution by dispensing pharmacists. The statute is clear on this point: the term interchangeable means "that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[10] As the Secretary of Health and Human Services put it in 2007, the point of the

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[7] *See generally* FDA, *Approved Prescription Drug Products with Therapeutic Equivalence Ratings, 35th Edition*, iv (2015) (*Orange Book*); *see also* Donald O. Beers & Kurt R. Karst, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements*, 14.02[B] (2015).

[8] 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 320.1(e). A therapeutic equivalence rating also requires that the drug product be adequately labeled and manufactured in compliance with current good manufacturing regulations. *See Orange Book* at vii.

[9] *Orange Book* at viii. FDA republishes these points in the preface of the *Orange Book* every year. It has also separately reminded both healthcare practitioners and pharmacists that it views therapeutically equivalent products as substitutable for their branded counterparts without prescriber involvement. *See, e.g.*, FDA, *Therapeutic Equivalence of Generic Drugs – Letter to Health Practitioners* (Jan. 28, 1998); FDA, *Therapeutic Equivalence of Generic Drugs – Response to Nat'l Ass'n of Boards of Pharmacy* (Apr. 16, 1997).

[10] 42 U.S.C. § 262(i)(3).

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legislation is for an interchangeable biological product to be "used in the same manner as therapeutically equivalent, generic drugs."[11]

C. Biological Products Differ Fundamentally From Small Molecule Drugs.

Biological products licensed under the PHSA are, as a scientific matter, fundamentally different from small molecule drugs approved under the Federal Food, Drug, and Cosmetic Act (FDCA). Small molecule drugs are usually chemically synthesized, simple, stable, homogenous, easily characterized, and easily replicable. Biological products, in contrast, are manufactured in living systems, significantly larger and more complex, difficult or sometimes impossible to fully characterize, always microheterogeneous, and highly sensitive to changes in raw materials and manufacturing conditions.[12]

A group of fifteen FDA officials—including the Director and Deputy Director of the Center for Drug Evaluation and Research (CDER) and the head of CDER's Office of Biotechnology Products—explained the differences between small molecule drugs and biological products in a pivotal article in *Nature Reviews Drug Discovery* in 2007. They wrote that protein products are, in contrast to small molecule drugs, "typically much larger, more complex molecules than non-protein, small molecule drugs" that "fold upon themselves and form specific conformations that can be critical to biological activity." Further, "protein products are often heterogeneous mixtures of molecules that vary slightly in molecular structure." The "quality and nature of natural-source products can also vary depending on factors such as variability of the source material (for example, time of year of harvest, species) and the processes used to extract and purify the product."[13]

These differences between small molecule drugs and biological products manifest themselves in two ways directly relevant to this Petition: (a) biological products are far more likely to be immunogenic than small molecule drugs, and (b) follow-on biological products cannot be shown to be the "same as" their reference products.

1. Immunogenicity

Unlike most small molecule drugs, biological products are recognized by the human immune system, and in some cases, this system may "attack" the biological product, producing

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[11] Ltr. from Health and Human Services Sec. Michael O. Leavitt to Sen. Edward M. Kennedy, 5 (June 26, 2007) (Leavitt Letter).

[12] Certain drugs approved under the FDCA are naturally derived or recombinant protein products, meet the new definition of biological product, and will be deemed licensed under the PHSA in 2020 pursuant to the transitional provisions of the BPCIA. *See* 42 U.S.C. § 262, note ("Products Previously Approved Under the Federal Food, Drug, and Cosmetic Act"). When this Petition refers to small molecule drugs, it is referring to the vast majority of drugs with approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), which are simple, easy to characterize, and chemically synthesized.

[13] Janet Woodcock *et al*., *The FDA's assessment of follow-on protein products: A historical perspective*, Nature Reviews Drug Discovery (Apr. 13, 2007).

antibodies in an attempt to protect the body. This response is referred to as immunogenicity and can lead to drastic, sometimes fatal, side effects in patients.[14] In some cases, immunogenicity can lead to a lack of effectiveness, including for patients who had previously been doing well on a biological product. Immunogenicity can also result in serious side effects.[15] FDA has noted that the "safety consequences of immunogenicity may vary wildly and are often unpredictable in patients administered therapeutic protein products."[16] Antibodies can also neutralize the body's own naturally occurring proteins, leading in some cases to life-threatening outcomes.[17]

For patients with serious, chronic diseases, immunogenicity can be particularly devastating because once a patient has developed a permanent, mature immune response to a particular active ingredient, that active ingredient can no longer be used by the patient. Immunogenicity can thus eliminate treatment options for patients.[18]

Immunogenicity can result from (1) product-specific factors and (2) patient-specific factors, and can be exacerbated through the switching of biological therapies. *Product-specific factors*—such as specific post-translational modifications, epitopes/antigenicity determinants, product aggregates, impurities with adjuvant activity, formulation components, and container closure systems—can increase or decrease the risk of immunogenicity,[19] which is why each biologics license application, including a biosimilar biological product application, should include a clinical assessment of immunogenicity.[20] *Patient-specific factors* can also increase or

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[14] *See generally* FDA, *Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products* (Aug. 2014) (Immunogenicity Guidance).

[15] *Id.* at 3.

[16] *Id.* The most serious possibilities are anaphylaxis, a cytokine storm, infusion reactions, and cross-reaction with an endogenous counterpart of the therapeutic product. Non-acute symptoms (such as fever, rash, arthralgia, myalgia, hematuria, proteinuria, serositis, central nervous system complications, and hemolytic anemia) also can occur. Although cytokine release syndrome (CRS) is not directly related to immunogenicity, *id.* at 4, it can be an acute phase reaction and can relate to the pharmacological activity of an antibody, so it is typically included as an immunogenic event. *See id.*; *see also, e.g.*, Daniel R. Getts *et al*., *Have we overestimated the benefit of human(ized) antibodies*, 2(6) mAbs 682, 683 (2010); Frank R. Brennan *et al*., *Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies*, 2(3) mAbs 233, 238 (2010).

[17] As an example, a small number of patients taking EPREX (recombinant human erythropoietin) (epoetin alfa) in the early 2000s developed neutralizing antibodies to all erythropoietin, including endogenous erythropoietin, which led to life-threatening pure red cell aplasia. *See* Katia Boven *et al*., *Epoetin-associated pure red cell aplasia in patients with chronic kidney disease: Solving the mystery*, 20(Supp. 3) Nephrol. Dial. Transplant iii33, iii34 (2005); *see also* Immunogenicity Guidance at 3.

[18] Suzanna M. Tatarewics *et al*., *Strategic characterization of anti-drug antibody responses for the assessment of clinical relevance and impact*, 6(11) Bioanalysis 1509 (2014); Thomas Pradeu *et al*., *The speed of change: Towards a discontinuity theory of immunity*, 13(10) Nature Reviews 764 (2013); Thierry Schaeverbeke *et al*., *Immunogenicity of biologic agents in rheumatoid arthritis patients: Lessons for clinical practice*, 53 Rheumatology 209 (2015).

[19] *See* Xing Wang *et al*., *Higher-order structure comparability: Case studies of biosimilar monoclonal antibodies*, 12(6) BioProcess International 32 (2014); *see also* Immunogenicity Guidance at 12-21.

[20] FDA has explained that a biosimilar applicant should assess "the nature of the immune response (*e.g.*, anaphylaxis, neutralizing antibody), the clinical relevance and severity of consequences (*e.g.*, loss of efficacy of life-

decrease the risk of immunogenicity. These patient-specific factors include concomitant medications, general immunologic status, age, prior exposure to the protein or structurally similar proteins, and genetic factors.[21] This means, in essence, that immunogenicity can vary from patient to patient, from population to population, and from indication to indication.[22]

Switching biological therapies can exacerbate immunogenicity. It has long been established that prior exposure to a biological product can affect the safety and efficacy of a later biological therapy, even where those biological products are in the same class (*e.g.*, IgG1 anti-tumor necrosis factor (TNF) antibodies). For example, when well-controlled infliximab Crohn's disease patients were switched to adalimumab, this switching was associated with "loss of tolerance and loss of efficacy within 1 year" when compared to patients who remained on infliximab therapy.[23] But the potential for loss of tolerance or efficacy when switching between even highly similar molecules, such as a reference product and a biosimilar, has also long been recognized as a risk.[24] Numerous professional[25] and regulatory[26] guidelines warn against

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saving therapeutic and other adverse effects), the incidence of immune responses, and the population being studied." Scientific Considerations Guidance at 16-18.

[21] Immunogenicity Guidance at 9-12.

[22] *See id.* For instance, the rate of immunogenicity associated with infliximab is said to range from 7% to 61% across indications. *See* Bradley J. Scott *et al*., *Biosimilar monoclonal antibodies: A Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation*, 55(S3) J. Clinical Pharmacology S123, S127 (2015).

[23] *See*, *e.g.*, Gert Van Assche *et al*., *Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: Prospective randomised SWITCH trial*, 61(2) Gut. 229 (2012).

[24] *See*, *e.g.*, Janet Woodcock, *Follow-on Protein Products*, Written Statement before the House Committee on Oversight and Government Reform (Mar. 26, 2007) (March 2007 Woodcock Testimony); Wolfgang Jelkmann, *Biosimilar epoetins and other "follow-on" biologics: Update on the European experiences* 85(10) Am. J. Hematol. 771, 773 (2010) ("The main concern about switching from one biological medicine to another is the issue of immunogenicity.").

[25] *See*, *e.g.*, Gionata Fiorino *et al*., *The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) Position Paper*, 13(7) Autoimmunity Reviews 751, 752 (2014) ("Currently, there are limited data on switching to a biosimilar in terms of maintenance of response, immunogenicity or other safety issues. Probably, in some cases, switching can be possible, but the final decision should be tailored on the patient by the clinician; in the case of automatic replacement, a certain risk of loss of response and loss of tolerance should be taken into account."); British Society for Rheumatology, *British Society for Rheumatology Position Statement on Biosimilar Medicines* (Feb. 2015), http://bit.ly/1EMxDug (noting that "there appears to be little evidence of the safety and effectiveness of switching to biosimilars in patients who are stable on a reference agent and a lack of knowledge of the long term safety of biosimilar drugs which may have subtly different immunogenic profiles" and recommending against "summarily switching all patients currently receiving a reference product that is effective and well tolerated to a biosimilar"); Lissy de Ridder *et al*., *Use of biosimilars in paediatric inflammatory bowel disease: A position statement of the ESPGHAN Paediatric IBD Porto Group*, 61(4) J. Pediatr. Gastroenterol. Nutr. 503, 507 (2015) (noting that children with a good response to a specific inflammatory bowel disease biological product should not be switched to a biosimilar absent clinical trials demonstrating safety and efficacy).

[26] *See*, *e.g.*, Bradley J. Scott *et al*., *Biosimilar monoclonal antibodies: A Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation*, 55(S3) J. Clinical Pharmacology S123, S130 (2014) (noting that one of Health Canada's concerns with interchangeability of biosimilars (which led to a

switching or alternating even highly similar biological products, at least in part, for this reason. The few studies that assess switching from a reference product to a biosimilar to date are limited in size, number of switches, and other trial design aspects. But at least some data suggest that switching has the potential to impact efficacy or safety, including immunogenicity.[27] And the threat may increase in the presence of multiple switches to and from a biological product.[28]

2. Sameness

Section 505(j) of the FDCA authorizes the approval of generic small molecule drugs based on the premise that a generic drug manufacturer can create an identical copy of a previously approved drug. Making this showing is relatively straightforward. As the FDA officials explained in their 2007 article, "the molecular structure of such a drug can usually be verified analytically," and consequently "it is fairly easy for a generic-drug manufacturer to produce a duplicate product containing an active ingredient that is the same as the active ingredient in an innovator's approved drug product."[29]

By way of contrast, Dr. Woodcock has testified repeatedly that "the idea of *sameness*. . . will not usually be appropriate for more structurally complex molecules of the type generally

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recommendation against automatic substitution) is that the "repeated switches between biosimilars and originator products may increase immunogenicity with potentially negative effects"); Ireland Health Products Regulatory Authority, *Guide to Biosimilars for Healthcare Professionals and Patients* (Oct. 2015), http://bit.ly/1N0SzAO ("It is not recommended that patients switch back and forth between a biosimilar and reference medicine, as at the current time the availability of data on the impact of this are limited.").

[27] Abstracts of the 51st Annual Meeting of the European Association for the Study of Diabetes, *Abstract #969: The Efficacy and Safety of LY2963016 Insulin Glargine in Patients with Type 1 and Type 2 Diabetes Previously Treated with Insulin Glargine* (showing that patients who were switched from the reference insulin product to the proposed biosimilar had higher rates of anti-drug-antibodies when compared to patients who remained on the reference insulin product); Abstracts of the 2013 American College of Rheumatology Annual Meeting, *Abstract #L15: Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13* (showing that patients who were switched from the reference infliximab product to the biosimilar experienced more adverse events when compared to patients who remained on the biosimilar). *But see, e.g.*, Abstracts of the 2015 European Crohn's and Colitis Organisation Annual Meeting, *Poster #295: Preliminary Assessment of Efficacy and Safety of Switching Between Originator and Biosimilar Infliximab in Paediatric Crohn Disease Patients* (assessing 32 Crohn's disease patients switched from the originator infliximab to the biosimilar infliximab and concluding that after one or two doses with the biosimilar, switching "seems to be safe").

[28] Martina Weise *et al*., *Biosimilars: What clinicians should know*, 120(26) Blood 5111 (2012) ("Another, more theoretical concern regarding automatic substitution is the possibility that repeated switches between the biosimilar and the reference product may increase immunogenicity with potentially negative effects on the safety and/or efficacy of the products. This would, however, also apply to switches between different originator biologicals of the same class. Automatic substitution may be difficult from a practical viewpoint, especially for patients self-administering the medicinal product, in case of differences in injection devices, preparation and handling of the biosimilar, which may increase the risk of medication errors or impair treatment compliance."); Janet Woodcock, *Biosimilar Implementation: A Progress Report from FDA*, Written Statement before the Subcommittee on Primary Health and Retirement Security (Sept. 17, 2015) ("[W]hat the concern has been is that this continued switching could raise that immunity – sort of provide a booster effect and cause untoward effects.").

[29] Woodcock, *supra* n.13.

licensed as biological products."[30] Dr. Woodcock has explained further: "Unlike small molecule drugs whose chemical composition can easily be determined to be the *same* as an approved product, the very nature of protein products makes comparisons of one protein to another, including comparisons to establish safety and efficacy, more scientifically challenging."[31] Indeed, "it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product."[32] Instead, Dr. Woodcock said, one would want "data and information showing the similarity of the products,"[33] *i.e.*, sufficient similarity to rely on the safety and efficacy findings made with respect to the reference product. This continues to be FDA's unqualified view, as expressed in recent final guidance.[34] That biosimilar and reference products are similar, but *not* identical, means one may not presume biosimilar and reference will have the same clinical effect in each condition of use approved for the reference product.

D. FDA May Designate A Biosimilar "Interchangeable" Only When It Has Been Shown To Be Interchangeable With Respect To Every Reference Product Condition Of Use.

Many innovative therapeutic proteins are approved to treat a diverse array of disease states, in a wide variety of patients, and under different conditions and instructions. For instance, Petitioner's product Humira (adalimumab) is licensed to treat a wide range of autoimmune disorders, including arthritic conditions (rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis), skin conditions (plaque psoriasis, hidradenitis suppurativa), and gastrointestinal conditions (adult and pediatric Crohn's disease, as well as ulcerative colitis). Each indication is accompanied by specific instructions regarding dose, frequency of administration, duration of use, type of therapy (*e.g.*, monotherapy, concomitant, first-line, second-line, etc.) and other relevant clinical considerations. These instructions combine to constitute the "conditions of use" for which the product is prescribed, recommended, or suggested within the meaning of both the FDCA and the PHSA.[35]

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[30] March 2007 Woodcock Testimony (emphasis added); May 2007 Woodcock Testimony.

[31] May 2007 Woodcock Testimony (emphasis added).

[32] *Id.*; *see also* Leavitt Letter at 5 (follow-on biological products "will not be the same as the reference product in the manner that generic drugs approved under section 505(j) are the same as the listed drug"); Ltr. from Frank M. Torti, M.D. to Frank Pallone, Jr., 4 (Sept. 18, 2008) (Torti Letter).

[33] May 2007 Woodcock Testimony.

[34] *See e.g.*, Scientific Considerations Guidance at 5 ("Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product.").

[35] The phrase "conditions of use" refers "to how, to whom, and for which purposes a drug product is used by physicians and patients." Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for Temporary Restraining Order and/or Preliminary Injunction, 20 (Apr. 17, 2012), Docket No. 22 in *Viropharma Inc. v. Hamburg*, No. 12-00584 (D.D.C.); *see generally id.* at 20-22; *see also* 21 U.S.C. § 321(p)(1) ("safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling"); 42 U.S.C. § 262(l)(2)(A)(iii) (the "conditions of use prescribed, recommended, or suggested in the labeling proposed for the [biosimilar]" must "have

As outlined below, FDA may not find a biosimilar product interchangeable with a reference product unless the agency has found the two products interchangeable for *every* condition of use for which the reference product is licensed, regardless of how the interchangeable biological product is labeled. Of course, an applicant may omit from the labeling of a biosimilar product one or more of the conditions of use appearing in the labeling of the corresponding reference product.[36] A biosimilar applicant might ask to do so, for example, if the reference product sponsor holds intellectual property covering the conditions of use in question. But as both a public health and legal matter, an interchangeability determination requires a showing that the "Safety Standards for Determining Interchangeability" set forth in PHSA section 351(k)(4) have been met for *every* condition of use for which the reference product is labeled.

1. Public Health

As described above, generic drugs are the "same" as their reference listed drug (RLD) counterparts. This means that generic drug applicants do not make indication-specific or population-specific showings in their applications, nor do they (or FDA) have to justify extrapolation of safety and effectiveness and interchangeability in one indication or population to a demonstration of safety and effectiveness and interchangeability in another indication or population. The standard for obtaining a therapeutic equivalence rating in the *Orange Book* for a generic drug is simply part of the standard for approval as a generic drug. That showing—pharmaceutical equivalence and bioequivalence—generally is sufficient as a scientific matter to predict that the generic drug will be equally safe and effective in *any* indication and condition of use for which the RLD is labeled, now or in the future. Therefore, once small molecule drugs are found pharmaceutically equivalent and bioequivalent, "they are assumed to be therapeutically equivalent," and it is thus "assumed that they are interchangeable."[37]

Although generic drug applicants sometimes omit conditions of use from their labeling,[38] their products remain therapeutically equivalent to the listed drug even for those omitted

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been previously approved for the reference product"); 21 C.F.R. § 201.100(c) (labeling for a prescription product must address "indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions"); FDA, *Guidance for Industry: ANDA Submissions—Refuse-to-Receive Standards*, 14-15 (May 2015) ("Examples of proposed condition of use changes may include, but are not limited to . . . . producing a capsule that cannot be administered in the same manner as the RLD, or proposing alterations to either the amount of active ingredient delivered per dose or the dosing regimen such that neither are consistent with those described in the RLD labeling.").

[36] *See* 42 U.S.C. § 262(k)(2)(A) (indicating that an applicant need *not* make the biosimilarity showing with respect to *every* reference product condition of use, by referring to performing the necessary clinical study in "1 or more appropriate conditions of use"); *see also* FDA, *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, 8 (Apr. 2015).

[37] Hans C. Ebbers *et al.*, *Interchangeability, immunogenicity, and biosimilars*, 30 Nature Biotech. 1186, 1188 (2012).

[38] The FDCA generally requires the generic drug's labeling to be the same as the labeling of its reference product, but it permits conditions of use to be carved out to avoid infringement of intellectual property rights. 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.92(a)(1) (allowing a generic applicant to carve out "conditions of use for which

conditions of use.[39] As a practical matter, a pharmacist will substitute a generic drug without regard to the condition of use for which the RLD was prescribed. Neither federal nor state law requires a pharmacist to determine whether the prescribed use appears in the generic drug's approved labeling. We are not aware of this inquiry being part of any pharmacy standard practice, and the process of filling prescriptions at the pharmacy level is not structured to accommodate such inquiries. There is, indeed, no public health reason for the pharmacist to determine whether the dispensed drug is actually approved for the patient's condition; the generic is inherently therapeutically equivalent for all uses. Further, if there are multiple generic drug products, there is no particular public health reason to select one over another, or to differentiate based on labeling. The assignment of the same "A" rating for all generics and an RLD in the *Orange Book* means that all such products can be seamlessly substituted, each for any of the others.

Like therapeutic equivalence designations for drugs, interchangeability determinations for biological products are intended to facilitate substitution at the point of dispensing, thereby generating cost savings for the healthcare finance system.[40] State laws governing pharmacy substitution of biological products generally direct the pharmacist to dispense a biological product that FDA has found interchangeable with the reference product.[41] Neither federal nor state law requires the pharmacist to determine whether the product to be substituted is labeled for (let alone determined to be interchangeable for) the prescribed use in question.[42] The assumption of these state laws is that an interchangeable biological product is functionally the same as a generic drug—it is therapeutically equivalent for all uses.

FDA therefore needs to ensure that biological products listed as substitutable are *in fact* interchangeable for all indications and conditions of use for which the reference product is labeled and thus might be prescribed. Any other approach risks the possibility that a physician will prescribe the branded product and the pharmacist will dispense a biological product that is not interchangeable for the patient's condition. In 2010, the Director of CDER's Office of

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approval cannot be granted because of exclusivity or an existing patent"). A carve-out must not render the generic drug "less safe or effective than the listed drug for all remaining, nonprotected conditions of use." *Id.* § 314.127(a)(7).

[39] A labeling carve-out is not relevant to therapeutic equivalence and therefore will not prevent a therapeutic equivalence determination for a particular product. *See* 59 Fed. Reg. 50338, 50357 (Oct. 3, 1994) ("[T]he fact that a pioneer drug is labeled with a protected indication does not mean that generic copies of the same drug are not therapeutically equivalent to the pioneer.").

[40] State legislatures are beginning to amend their pharmacy laws to authorize substitution of interchangeable biological products, just as those laws currently authorize substitution of small molecule generic drugs. *See, e.g.*, Del. Code § 2549A; Fla. Stat. § 465.0252; Ind. Code § 16-42-25-4; Mass. Gen. Laws § 12EE; N.D. Cent. Code § 19-02.1-14.3; Or. Rev. Stat. § 689.522; Utah Code § 58-17b-605.5; Va. Code § 54.1-3408.04.

[41] *See, e.g.*, Fla. Stat. § 465.0252(2) ("A pharmacist may only dispense a substitute biological product for the prescribed biological product if: (a) The United States Food and Drug Administration has determined that the substitute biological product is biosimilar to and interchangeable for the prescribed biological product . . . .").

[42] *Compare, e.g., id., with* Fla. Stat. § 465.025(2) ("A pharmacist who receives a prescription for a brand name drug shall, unless requested otherwise by the purchaser, substitute a less expensive, generically equivalent drug . . . .").

Medical Policy acknowledged that, if a product is determined to be interchangeable, a presumption will arise that the product is "interchangeable for all indications."[43] For precisely these reasons, other stakeholders have similarly advocated to FDA that applicants seeking interchangeability determinations must demonstrate interchangeability with respect to all conditions of use for which the relevant reference product is labeled.[44]

2. Statutory Text And Structure

Section 351(k)(4)(A) permits an interchangeability determination only if the biological product in question is biosimilar and (separately) "can be expected to produce the same clinical result as the reference product *in any given patient*."[45] As the Supreme Court has explained, "the word 'any' has an expansive meaning, that is, 'one or some indiscriminately of whatever kind.'"[46] Further, "given" means "known; stated; [or] specified."[47] When paired together, the words "any given" take on an extraordinarily broad, idiomatic meaning akin to "every" or "all" (*e.g.*, "on any given Sunday" or "at any given time").[48] Thus, the plain meaning of "any given patient" in section 351(k)(4)(A) is all known, stated, or specified patients. Further, because it is juxtaposed with "the reference product," the phrase "any given patient" must be understood to mean all patients for whom the reference product is known, stated, or specified. Under the plain terms of section 351(k)(4)(A), therefore, a biological product can be deemed interchangeable only if it can be expected to produce the same clinical result as the reference product in any patient for whom the reference product is specified—meaning any patient covered by any approved reference product condition of use.

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[43] Transcript of Part 15 Public Hearing on Approval Pathway For Biosimilar and Interchangeable Biological Products, 227:17-21 (Nov. 2, 2010).

[44] *See, e.g., id.* at 232:17-20 ("[F]rom a practical perspective, interchangeability, we believe, would need to be established for each reference product indication.") (statement of Dr. F. Owen Fields, Pfizer); Transcript of Part 15 Public Hearing on Approval Pathway For Biosimilar and Interchangeable Biological Products, 323:2-8 (Nov. 3, 2010) (noting that FDA should require an applicant to show interchangeability "for all indications of the reference product" because "once it is on the market it will be used interchangeably for all indications by physicians and pharmacists") (statement of Dr. Marie Vodicka, PhRMA); *id.* at 342:17-343:1 (" If an interchangeable biosimilar is approved, it is likely to be used interchangeably for all indications by pharmacists and physicians.") (statement of Sara Radcliffe, BIO); *see also, e.g.*, Comments of Amgen Inc., Docket No. FDA-2010-N-0477, 40 (Dec. 29, 2010) ("A biosimilar should not be deemed interchangeable unless it has been shown to be interchangeable for all routes of administration and all indications of the reference product because in real-world use, it will likely be interchanged for all uses once the designation is made."); Comments of Johnson & Johnson, Docket No. FDA-2010-N-0477), 8 (Dec. 23, 2010) ("Biosimilars should not receive interchangeability designations unless they have been found to meet the interchangeability standard with respect to every approved indication of the reference product.").

[45] 42 U.S.C. § 262(k)(4)(A)(ii) (emphasis added).

[46] *Ali v. Fed. Bureau of Prisons*, 552 U.S. 214, 219 (2008) (quoting *United States v. Gonzales*, 520 U.S. 1, 5 (1997) (quoting Webster's Third New International Dictionary 97 (1976))).

[47] Webster's New Universal Unabridged Dictionary, 773 (1983).

[48] *See* Longman Dictionary of Contemporary English ("any particular, time, situation, amount, etc. that is being used as an example"), http://www.ldoceonline.com/dictionary/given_2 (last visited Dec. 4, 2015).

This plain meaning of section 351(k)(4)(A) is buttressed by language elsewhere in the statute, in particular language in sections 351(k)(2)(A), (k)(4)(B), and (k)(6).

As an initial matter, the interchangeability standard in (k)(4)(A) expressly differs from the requirements set out in (k)(2)(A) for an application seeking licensure of a *non-interchangeable* biological product. An applicant seeking approval for a *non-interchangeable* biological product clearly does *not* need to show biosimilarity with respect to every reference product condition of use. Specifically, subsection (k)(2)(A) refers to a biosimilar applicant including in its BLA clinical studies "to demonstrate safety, purity, and potency in *1 or more* appropriate conditions of use."[49] The interchangeability standard in (k)(4)(A) lacks this language. Moreover, the interchangeability standard *adds* language referring to "the same clinical result . . . in any given patient." Sections (k)(4)(A) and (k)(2)(A) must be harmonized,[50] and the most logical harmonized reading is that a biosimilarity license permits a demonstration in only one condition of use, while an interchangeability determination requires that every condition of use be addressed.

This interpretation is reinforced by the language in section 351(k)(4)(B), which imposes an even higher standard for showing interchangeability if the reference product is intended to be administered more than once to an individual, *e.g.*, as a medication used to treat a chronic condition. The relevant language states that the applicant must show that the risk to patients of alternating or switching between "use of the biological product and the reference product" is no greater than the risk of "using the reference product" alone.[51] This provision of the statute does not qualify "use" in any manner. It is hard to see how this standard could be met unless the applicant had addressed "use" of the reference product broadly, *i.e.*, in all approved reference product conditions of use.

Finally, the plain meaning of section 351(k)(4) is fully consistent with section 351(k)(6), which provides a period of exclusivity for the first biological product to be approved as interchangeable as to "any condition of use" of the reference product.[52] This provision does not mean that an applicant may demonstrate interchangeability for a subset of conditions of use approved for the reference product. Rather, it simply admits the possibility of labeling carve outs.[53] The thrust of section 351(k)(6) is that the first-in-time interchangeable biological product will be entitled to a period of exclusivity against a subsequent interchangeable product, even if

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[49] 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc) (emphasis added).

[50] *Cf. Russello v. United States*, 464 U.S. 16, 23 (1983) ("Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.") (citation omitted).

[51] 42 U.S.C. § 262(k)(4)(B).

[52] Under section 351(k)(6), once a biological product's sponsor has received a determination that the product is interchangeable with its reference product, FDA will not deem another product interchangeable with that reference product until one year after first commercial marketing or eighteen months after approval, whichever is earlier (unless there is patent litigation, in which case the length of time changes). *See* 42 U.S.C. § 262(k)(6).

[53] *See supra* text accompanying n.39.

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the two products are labeled for different subsets of the reference product's conditions of use. It remains the case, however, that any applicant seeking an interchangeability determination must demonstrate interchangeability for every approved reference product condition of use.

3. Legislative History

Although recourse to legislative history is not necessary where, as here, a statute's meaning is plain, the legislative history of the BPCIA further supports the conclusion that Congress intended an applicant to demonstrate interchangeability for all of the reference product's licensed conditions of use. The first biosimilar bills, introduced in the fall of 2006, would have permitted an applicant to make a selective showing of interchangeability. Specifically, these bills would have required that an applicant seeking an interchangeability determination show that its product could be expected to produce "the same clinical result in any given patient in the condition or conditions of use *for which both products are labeled*."[54] But, by the spring of 2007, revised bills had been introduced that would have required an applicant for interchangeability to show that its product was expected to produce "the same clinical result as the reference product in any given patient."[55] The language permitting a selective showing had been dropped.

Further, in 2007, the Administration released a letter from the Secretary of Health and Human Services to Senator Kennedy stating that, if a sponsor seeks an interchangeability determination, "it should be required to do so for all conditions of use for which the reference product is approved."[56] Secretary Leavitt explained that the absence of such a requirement "creates a very real safety hazard . . . that a patient might be switched to a product for an indication that had never been demonstrated to be either biosimilar or interchangeable."[57] The version of the legislation reported by the Senate Committee on Health, Education, Labor and Pensions in late 2008, and the House and Senate bills that eventually became law, used the phrase "any given patient" without including any language that would have permitted a selective showing of interchangeability.[58]

This history compels the conclusion that Congress rejected the option for applicants to make selective interchangeability showings. If Congress "includes limiting language in an earlier version of a bill but deletes it prior to enactment, it may be presumed that the limitation was not intended."[59]

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[54] S. 4016, 109th Cong. (2006) (emphasis added); H.R. 6257, 109th Cong. (2006) (same).

[55] S. 623, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007) (same).

[56] Leavitt Letter at 6.

[57] *Id.*

[58] *See* S. 1695, 110th Cong., 48 (2008); H.R. 5629, 110th Cong. (2008); H.R. 1548, 111th Cong. (2009); S. 1679, 111th Cong., 780 (2009); Amendment No. 2786 to H.R. 3590, 111th Cong., 1864 (2009).

[59] *Russello*, 464 U.S. at 23-24 (citation omitted).

4. Post Interchangeability Determination Product Changes

The requirement to take into consideration all conditions of use approved for the reference product in making interchangeability determinations means that FDA will need to consider the impact of changes made to either the reference product or the interchangeable biological product after an interchangeability determination has issued. For instance, the reference product sponsor may obtain approval of new indications or conditions of use after interchangeability has been established. FDA needs to consider the impact of these changes on interchangeability because the public health considerations identified in this Petition are as relevant to subsequent conditions of use as they are to conditions of use of the reference product approved at the time interchangeability was first determined.

AbbVie believes that a previously issued interchangeability determination should not be disturbed absent significant scientific questions regarding the continuing validity of the determination following a product change. We believe that the *Orange Book* preface points to a path forward for handling these situations that will respect the law, adequately protect the public health, and minimize disruption to established products and markets. The *Orange Book* suggests that therapeutic equivalence ratings for generic drugs may be changed, but *only* "as a result of new information raising a significant question as to bioequivalence."[60] Applying a similar approach in the BPCIA context, a previously issued interchangeability determination for a biological product would not be altered unless a manufacturing change or a new condition of use raises significant scientific questions (that were not answered satisfactorily) about the continuing validity of the determination. This, AbbVie believes, should be a rare occurrence.

E. The Statutory Standards For Interchangeability And Biosimilarity Differ.

As described above, an applicant seeking an interchangeability determination for its biological product must establish interchangeability with respect to every condition of use for which the reference product is licensed. The showing in question entails a demonstration that, as to each condition of use, (1) the biological product is biosimilar to its reference product *and* (2) "can be expected to produce the same clinical result as the reference product in any given patient," *and further* (3) in the case of a biological product administered more than once to a patient, "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."[61] As explained below, these showings differ in both kind and scope from the showing necessary for approval as a biosimilar.

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[60] *See Orange Book* at xxiv (discussing a change in therapeutic equivalence ratings from "AB" to "BX").

[61] 42 U.S.C. § 262(k)(4)(A)(i)-(ii), (k)(4)(B). Because a biological product must be shown interchangeable for all conditions of use approved for the reference product, if the applicant did not establish biosimilarity with respect to a particular condition of use in its initial application, it will need to do so when it subsequently seeks an interchangeability designation. This naturally follows from the statutory structure, which establishes biosimilarity as a required element of an interchangeability determination.

To begin with, as a matter of statutory construction, interchangeability must be interpreted to require more than biosimilarity. Section 351(k)(4)(A)(ii) ("can be expected to produce the same clinical result as the reference product in any given patient") must be read to require something in addition to and different from section 351(k)(4)(A)(i) ("is biosimilar to the reference product"). Establishing that a biological product "can be expected to produce the same result as the reference product in any given patient" must, as a matter of law, mean something *other than* biosimilarity.

Furthermore, section 351(k)(4)(A)(ii) explicitly asks the applicant to answer scientific questions not encompassed within the statutory standard for biosimilarity. First, the applicant must show that the products can be expected to produce the "same clinical result" in any given patient. This language is different from the "no clinically meaningful differences" language Congress used to describe biosimilarity,[62] and must represent a more exacting standard—for example, slight differences in the timing or magnitude of clinical response that might not necessarily be considered "significant" would be barred under this standard. Second, the requirement to reach a conclusion applicable to "any given patient" is novel.[63] By way of contrast, other product approvals, including biosimilar approvals, represent a conclusion that, at a *population* level, the benefits of the product outweigh the risks of the product when used as labeled.[64] At a minimum, a conclusion with respect to "any given patient" requires a different statistical design than used in biosimilar applications not seeking interchangeability determinations.

The next interchangeability provision, section 351(k)(4)(B), establishes a third, distinct requirement for an interchangeability determination sought "for a biological product that is administered more than once to an individual." This provision is similarly joined to the

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[62] *Compare* 42 U.S.C. § 262(k)(4)(A)(ii) *with* 42 U.S.C. § 262(i)(2)(B); *see also* Robert Temple, *A regulator's view of CER*, 9(1) Clin. Trials 56, 57 (2011) (noting that sameness or "equivalence" is the generic drug approval standard and what "is clear is that 'no significant difference' or a demonstration of [non-inferiority] is not the same as equivalence."). Indeed, biosimilarity—which requires a showing of "no clinically meaningful difference"—may be established in some cases simply with a showing of non-inferiority in an appropriate study population. *See* Scientific Considerations Guidance at 20.

[63] *Compare* 42 U.S.C. § 262(k)(4)(A)(ii) *with* 21 U.S.C. § 355(b), (d) (requiring that a new drug be safe for use under conditions suggested in the labeling and that there be substantial evidence that it will have the effect suggested in the labeling); 42 U.S.C. § 262(a) (requiring that a biological product be safe, pure, and potent); 21 U.S.C. § 360e(c), (d) (requiring a reasonable assurance of safety and effectiveness for medical devices). None of these provisions suggests assessment at the individual patient level.

[64] *See, e.g.*, FDA, *FDA's Overall Risk Management Activities* (Sept. 16, 2009), http://1.usa.gov/1kshowa ("A risk/benefit analysis is integral to FDA's review process for medical products: approval for marketing follows a determination that a product's benefits outweigh the risks associated with its labeled use for the intended population."); John Jenkins, M.D., *A United States Regulator's Perspective on Risk-Benefit Considerations*, Slide 10 (Apr. 23, 2010), http://1.usa.gov/1MqwHfF ("Regulators make judgments on B/R at the population level"); Tarek A. Hammad *et al*., *The future of population-based postmarket risk assessment: A regulator's perspective*, 94(3) Clin. Pharmacol. Ther. 349 (2013) ("Drug regulation rests primarily on a population-based approach that seeks to ensure that, on a population level, the benefits of a drug exceed its risks."). This is true of the biosimilar application, as well as innovative applications, because the reference product application made a population level showing, and the biosimilar application relies on that finding; it does not address safety and effectiveness *de novo*.

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preceding subsections by "and"; thus, it specifies something additional and different from the separate showings required by subsections 351(k)(4)(A)(i) and (ii).

Section 351(k)(4)(B) requires an evaluation of the risks, including the risks of diminished efficacy, presented by a switch from one product to the other and by alternating between the products, *i.e.*, switching back and forth. In other words, (k)(4)(B) requires full evaluation of safety and effectiveness in two *new* scenarios that were not addressed in either the reference product application or the initial biosimilar application. Further, it imposes a higher burden of proof than 351(k)(4)(A)(ii). That provision requires a showing that the proposed product *"can be expected"* to produce the same clinical result in any given patient, but section 351(k)(4)(B) requires a showing that the risk of alternating or switching *"is not"* greater than the risk of using the reference product alone. The "is not" language compels a more definitive showing than the "can be expected" language, which means that the applicant will need to establish near-certainty with respect to the comparative risk conclusion, which has implications for study design and statistical method.

The high standard in 351(k)(4)(B) is essential because, as noted earlier, the immunogenicity of biological therapies may be exacerbated by switching or alternating among products.[65] There are many patients with debilitating chronic or potentially life-threatening diseases stabilized on a particular biological product therapy and these patients, switched inappropriately, may risk a severe side effect, a loss of efficacy, or both. These risks could increase if the patient was switched inappropriately back to the original or to a third biological product. And, for some patients, including those with Crohn's disease and ulcerative colitis, a potential immune reaction caused by inappropriately switching or alternating could be particularly devastating because of the small number of non-surgical treatment options. Section 351(k)(4)(B) thus requires virtual elimination of the risk that a patient repeatedly switching between two biological products will experience an enhanced or different immunogenic response to one or the other product.

All told, the statute imposes a licensure standard for interchangeability that requires an unprecedented level of certainty, showing that any patient taking the reference product for any condition of use would not experience any change in his or her outcome as a result of switching back and forth multiple times to the biosimilar. This conclusion is bolstered by the fact that Congress provided exclusivity for the first applicant to obtain an interchangeability determination.[66] One year of exclusive positioning as the sole substitutable alternative to the reference product would not have been a necessary incentive unless Congress had intended to require applicants to invest substantially more research and development resources establishing interchangeability than they invested for initial licensure as a biosimilar.

These standards for determining interchangeability cannot presently be met with analytical testing alone given, at a minimum, the limitations of analytics in predicting

[65] *See supra* at notes 22-28, and accompanying text.

[66] *See* 42 U.S.C. § 262(k)(6).

immunogenicity.[67] Rather, an interchangeability demonstration will require clinical testing, as FDA officials have signaled repeatedly. FDA officials wrote in 2007 that an applicant would need to demonstrate "through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity."[68] Dr. Woodcock has twice testified about the need for "clinical data that repeated switches from the follow-on product to the referenced product (and vice versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity."[69] Moreover, this clinical testing will need to account for the fact that, as FDA has noted, immunogenicity depends on patient-specific factors, including age, genetic makeup, the pathophysiology of the treated disease, concomitant therapies, concomitant disease, immunologic status, and prior exposure to the protein and/or structurally similar proteins.[70]

F. Interchangeability Guidance

CDER has indicated since at least January 2014 that it intends to issue biological product interchangeability guidance for industry, but to date no such guidance has been released.[71]

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[67] *See generally* Immunogenicity Guidance at 21-22 (noting that immune responses to therapeutic protein products cannot be predicted based solely on risk factors pertaining solely to quality attributes and patient/protocol factors, and therefore should be "evaluated in the clinic"); *see* 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc) (requiring a clinical study or studies "including the assessment of immunogenicity"). These concerns are not merely theoretical; unforeseen observed immunogenicity with respect to certain individual biological products has been attributed to changes in post-translational modifications that either were not detected or were not initially predicted to be clinically significant. *See* EMA, *Omnitrope: EPAR – Scientific Discussion*, 2-3, 5 (2006) (noting immunogenicity issues during the development of Omnitrope that were later attributed to excess host cell protein contamination caused during the purification process); Andres Seidl *et al*., *Tungsten-induced denaturation and aggregation of epoetin alfa during primary packaging as a cause of immunogenicity*, 29(6) Pharm. Res. 1454, 1554-57 (2012) (detailing the unexpected increased immunogenicity in patients receiving epoetin alfa and attributing this increased immunogenicity to the syringe-manufacturing process for the product); Bruce Strober *et al*., *Biopharmaceuticals and biosimilars in psoriasis: What the dermatologist needs to know*, 66(2) J. Am. Acad. Dermatology 317, 319-320 (2012) (detailing variations in pharmacokinetic properties and FDA's concomitant concern with switching production of Raptiva (efalizumab) to a new manufacturing facility); George Mack, *FDA balks at Myozyme scale-up*, 26(6) Nature Biotechnology 592 (2008) (describing FDA's concerns with Genzyme's proposal to manufacture Myozme (alglucosidase alfa) in a 2000-liter-scale facility when the original application covered manufacture only at Genzyme's 160-liter-scale plant); Endocrinologic and Metabolic Drug Advisory Committee Meeting, *Clinical Background Materials* 38 (Oct. 21, 2008) (observing that Myozme (alglucosidase alfa) manufactured in 2000-liter-scale production presented the "potential for increased immunogenicity" when compared to product manufactured in 160–liter-scale production); Katia Boven *et al*., *The increased incidence of pure red blood cell aplasia with an Eprex formulation in uncoated rubber stopper syringes*, 67(6) Kidney Int'l 2346 (2005) (concluding that changes to the type of rubber stopper used in prefilled Eprex syringes was "the most probable cause of the increased immunogenicity" that led to several instances of pure red blood cell aplasia).

[68] Woodcock, *supra* n.13.

[69] March 2007 Woodcock Testimony; May 2007 Woodcock Testimony.

[70] Immunogenicity Guidance at 9-12.

[71] *See, e.g., Guidance Agenda: New & Revised Guidances CDER is Planning to Publish During Calendar Year 2014* (Jan. 31, 2014).

AbbVie believes that a public and transparent discussion of the relevant issues will best facilitate the development of sound regulatory policies regarding the interchangeability provisions of the BPCIA.

Any FDA guidance on BPCIA interchangeability determinations should address the real-world possibility that different interchangeable biological products corresponding to a single reference product will be substituted and switched over the course of a single patient's treatment. This is routine pharmacy and payor practice with respect to generic small molecule drugs. Upon approving a generic drug, FDA deems the generic to be "A"-rated to its RLD. Further, as more generic copies of a particular reference product are approved, each one is designated "A" in the *Orange Book*, indicating as a practical matter to dispensing pharmacists that all generics with the same "A" rating are interchangeable with each other, in addition to being interchangeable with the reference product. As a result, over a course of treatment with multiple refills, a patient may receive some or all of the possible generic substitutes for the prescribed product, in any order, with or without repetition. This is medically appropriate for small molecule drugs because each generic is the same as, and therapeutically equivalent to, the reference product and each other, and because switching and alternating does not *itself* trigger any safety or effectiveness concerns.

In contrast, a patient alternating among biological products may, as a result of the alternating itself, experience an enhanced or different immunogenic response to one or another of the products. At this time, however, there is no reason to think that state pharmacy practices with respect to interchangeable biological products will be different from practices with respect to generic drugs. That is to say, pharmacists and patients will presume that interchangeable biological products are interchangeable not only with the reference product but also *with each other*. Indeed, the emerging state pharmacy laws could be read to permit the dispensing pharmacist to dispense any interchangeable biological product for the prescribed reference product, without taking into account which—or how many different—product(s) have previously been administered.[72] As a public health matter, particularly because most biological products are administered more than once, leading to long-term therapy in some cases, FDA should address the issue now, when setting the standard for interchangeability determinations for chronic therapies.

G. FDA Should Convene A Part 15 Hearing.

AbbVie submits that "it is in the public interest to permit persons to present information and views at a public hearing" regarding the interchangeability of biological products.[73] In 2010 and again in 2012, the Agency convened public meetings to discuss the implementation of the BPCIA.[74] Those meetings—and particularly the second—focused on the implementation of the

[72] The Secretary of Health and Human Services raised concerns about switching among interchangeable products during the legislative process. *See* Leavitt Letter at 6 (suggesting that any applicant seeking the interchangeability designation should demonstrate interchangeability to the reference product and any other product already deemed interchangeable to the reference product).

[73] 21 C.F.R. § 15.1(a).

[74] *See* 75 Fed. Reg. 61497 (Oct. 5, 2010); 77 Fed. Reg. 12853 (Mar. 2, 2012).

BPCIA's biosimilar pathway. Questions regarding the BPCIA's interchangeability provisions were largely left for another day.[75]

Given the passage of time, it is appropriate to convene another Part 15 hearing regarding the implementation of the BPCIA's interchangeability provisions.[76] Public input from all relevant stakeholders—not just manufacturers, but also patients, prescribers, pharmacists, payors, and others—will help ensure that interchangeable biological products are introduced in a fashion that best serves the public interest and the public health.

H. Conclusion

For the reasons discussed above, AbbVie requests that FDA recognize, both as a public health policy and as a legal matter, that an applicant seeking an interchangeability designation for its biological product must establish interchangeability with respect to *each* condition of use for which the reference product is licensed, whether or not the follow-on biological product will be licensed and labeled for that condition of use. We further urge FDA to acknowledge that the statutory standard for establishing interchangeability differs in both kind and scope from the standard for establishing biosimilarity. Finally, we request that FDA address the scientific and public health issues set forth in section III.F as it considers implementing the interchangeability provisions of the BPCIA, and that it do so based in appropriate part on input from a public hearing convened under 21 C.F.R. Part 15.

III. OTHER REQUIRED INFORMATION

A. Environmental Impact

The actions requested in this Petition are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

B. Economic Impact

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

[75] 77 Fed. Reg. at 12854 (noting that interchangeability was "currently under consideration for future guidance").

[76] We are not alone in urging FDA to convene a new Part 15 hearing regarding the BPCIA. A recent citizen petition regarding biosimilar labeling made a similar request. *See* Docket No. FDA-2015-P-4529.

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C. Certification[77]

I certify that, to my best knowledge and belief: (a) this Petition includes all information and views upon which the Petition relies; (b) this Petition includes representative data and/or information known to the Petitioner which are unfavorable to the Petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the Petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this Petition is submitted on or about the following date: January 31, 2014. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: AbbVie Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this Petition.

Respectfully Submitted,

Perry C. Siatis/dk

Perry C. Siatis
Vice President
Biotherapeutics and Legal

Neal Parker

Neal Parker
Section Head
Legal Regulatory

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[77] This Petition asks FDA to adopt a particular regulatory approach with respect to interchangeability determinations pursuant to section 351(k)(4) of the PHSA, which, to date, is not the subject of any regulation or published guidance. To the best of our knowledge, no applicant has yet submitted to FDA a BLA seeking licensure as an interchangeable biological product. For either reason, this Petition is not subject to section 505(q) of the FDCA. Nevertheless, and out of an abundance of caution, we have included the certification required by that provision.