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May 19, 2017

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Re: Docket No. FDA-2017-D-0154, Considerations in Demonstrating Interchangeability With a Reference Product; Draft Guidance for Industry; Availability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:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments on the Food and Drug Administration's (FDA's or the Agency's) draft guidance entitled "Considerations in Demonstrating Interchangeability with a Reference Product" (draft guidance).[1] PhRMA represents the country's leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures, with members investing an estimated $58.8 billion in 2015 in the discovery and development of new medicines. Importantly, many of PhRMA's members are actively researching and developing new biosimilar products to bring to patients.

PhRMA supported the enactment of the Biologics Price Competition and Innovation Act (BPCIA) and has actively participated in FDA's ongoing efforts to implement the statute. We applaud FDA's issuance of the draft guidance and appreciate the Agency's consideration of these comments. Although the draft guidance provides welcome insights into FDA's current thinking, the draft guidance would benefit from several revisions.

First, the guidance should further explain the distinction between biosimilarity and interchangeability. In particular, the guidance should note that interchangeability is a high standard that requires additional data beyond what is required to show biosimilarity.[2] The guidance also should clarify the implications of an interchangeability determination—i.e., the product is interchangeable with the reference product, but not other biosimilar or interchangeable products—and address the differences between therapeutic equivalence and

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[1] 82 Fed. Reg. 5579 (Jan. 18, 2017).

[2] *See* Public Health Service Act (PHSA) § 351(k)(4); *see also* PhRMA Comment, Docket No. FDA-2010-N-0477-0036, at 9-10 (Dec. 23, 2010) (PhRMA 2010 Comments). This reference to a "high standard" for interchangeability is not intended to suggest that there is a difference in quality between products licensed as biosimilar but not interchangeable and products licensed as interchangeable biosimilars.

interchangeability. The guidance also should confirm that, as a matter of law, interchangeability determinations will not be possible until March 23, 2020 for follow-on versions of transition biological products, i.e., those biologics submitted and approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA).

Second, the guidance should provide additional detail on the data and information needed to establish interchangeability. More specifically, FDA should describe the conditions under which interchangeability may be established in an original biologics license application submitted under section 351(k) of the Public Health Service Act (PHSA). FDA also should clarify the circumstances under which postmarketing data are needed to show interchangeability and what types of postmarket data are needed. Moreover, FDA should consider recommending other statistical approaches for analyzing pharmacokinetic (PK) data that assess subject-by-formulation interaction variance to demonstrate that an interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient."[3]

PhRMA also requests that the guidance provide further recommendations on the design of switching studies. In particular, because PK and pharmacodynamic (PD) assessments might not capture all clinically relevant differences between a proposed interchangeable product and reference product, PhRMA believes that switching studies also generally should include a robust assessment of efficacy and immunogenicity. We also recommend that the guidance explain the type of scientific justification that would be necessary for a non-U.S.-licensed comparator to be used in switching studies and clarify the meaning of "meaningful fingerprint-like characterization."[4] Also, the guidance should state explicitly that FDA will, in assessing threshold analyses and data requirements based on the presentation of a proposed interchangeable product, consider whether patients who have long experience with the reference product presentation are at a higher risk of use-related error from presentation differences.

Third, we suggest revisions to strengthen the recommendation that sponsors of proposed interchangeable products demonstrate interchangeability for all conditions of use approved for the reference products. It should be recognized that this recommendation does not mean that sponsors need to conduct clinical studies for all such conditions of use. The guidance also should address situations when FDA approves a new condition of use for the reference product after FDA licenses a biologic as interchangeable with that reference product. The guidance should recommend that the sponsor of the interchangeable product scientifically justify the interchangeability of its product as to the new condition of use to maintain the product's designation as an interchangeable product. This scientific justification could entail extrapolation, and PhRMA expects that changes to interchangeability status based on new conditions of use would be rare.

Finally, PhRMA requests that FDA provide guidance on naming and labeling issues for interchangeable products and on exclusivity for first interchangeable biological products. PhRMA recommends that the nonproprietary name of an interchangeable product should be distinguished from that of the reference product and other interchangeable products through a unique suffix. We also request that biosimilar labeling state whether or not FDA has made a

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[3] PHSA § 351(k)(4)(A)(ii).

[4] *See, e.g.*, Draft Guidance, at 6.

determination of interchangeability with the reference product and include any such FDA finding, in addition to a definition of interchangeability. Moreover, we ask that FDA describe how it will determine which interchangeable product(s) will receive exclusivity under section 351(k)(6) of the PHSA if multiple applications for interchangeability are submitted and ready for approval on the same day. Last, we recommend that FDA develop a policy to address the regulation of post-approval manufacturing changes for interchangeable products.

I. The Guidance Should Address the Distinction Between Biosimilarity and Interchangeability and Clarify Other Key Concepts.

PhRMA urges FDA to further address the distinction between biosimilarity and interchangeability, to help prevent inappropriate substitution of non-interchangeable products. The guidance also should clarify the differences between therapeutic equivalence and interchangeability and address the eligibility of follow-on versions of transition biological products for interchangeability determinations.

For many years, FDA has highlighted the safety and effectiveness concerns that may arise from immunogenicity if patients switch back and forth between non-interchangeable biological products.[5] To ensure that switching between a proposed interchangeable product and reference product does not raise such safety or efficacy issues, section 351(k)(4) of the PHSA requires interchangeable biosimilar products to meet a high standard that involves two additional showings beyond biosimilarity.[6] First, an applicant must show that the proposed interchangeable biosimilar "can be expected to produce the same clinical result as the reference product in any given patient."[7] For a multiuse product, the applicant also must establish that "alternating or switching" will not increase the risk, in terms of safety or diminished efficacy, compared to using the reference product alone.[8]

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[5] *See, e.g., Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. 33 (2007) (statement of Janet Woodcock, M.D.) ("[T]here is a significant potential for repeated switches between products to have a negative impact on . . . safety and/or effectiveness" as a result of immunogenicity); 80 Fed. Reg. 52224, 52226 (Aug. 28, 2015) ("Inadvertent switching between biological products that have not been shown to be interchangeable may affect immune response" and "can lead to significant clinical consequences, such as pure red cell aplasia; inhibition of the efficacy of therapeutics; and reactions, including serum sickness and anaphylaxis."); Letter from Frank M. Torti, M.D., M.P.H., FDA Principal Deputy Commissioner & Chief Scientist, to Hon. Frank Pallone, Jr., Chairman, Subcomm. on Health, H. Comm. on Energy & Commerce, at 3 (Sept. 18, 2008) (FDA's "paramount concern is that patients not be exposed to an avoidable safety risk by being switched to a product not known to be interchangeable with the product they are currently receiving."); Mari Serebrov, *Don't Call Them Generics!*, BioWorld Perspectives (Jan. 29, 2013), http://www.bioworld.com/perspectives/2013/01/29/dont-call-them-generics/ (stating that FDA's Dr. Rachel Sherman's "worst nightmare would be for a formulary, seeing a big price difference, to treat biosimilars as it would a generic and switch everyone from the reference product to the biosimilar.").

[6] As noted, this reference to a "high standard" for interchangeability is not intended to suggest that there is a difference in quality between products licensed as biosimilar but not interchangeable and products licensed as interchangeable biosimilars.

[7] PHSA § 351(k)(4)(A).

[8] *Id*. § 351(k)(4)(B).

Although the draft guidance recites these statutory standards, there remains a need to further educate prescribers, pharmacists, patients, payers, and other stakeholders about the distinction between interchangeable and non-interchangeable biosimilar products. We ask that FDA take this opportunity to expressly state that interchangeability is a high standard that requires additional data beyond what is needed to show biosimilarity. Interchangeable products will be subject to pharmacy-level substitution as provided by state law without the clinical judgment and intervention of the treating physician, and therefore, stakeholders need confidence that switching or alternating will not compromise patients' disease stability. Further, the Agency should clarify that a non-interchangeable biosimilar product should not be substituted at the pharmacy level for the reference product without the intervention of the prescriber.[9] To convey this point, PhRMA recommends that FDA include in the guidance a statement like the one that appears on the Agency web page containing links to the Purple Book: "FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level [without the intervention of the prescriber]."[10] PhRMA also requests that biosimilar labeling state whether or not a product has been determined by FDA to be interchangeable with the reference product and include any such finding as well as a definition of interchangeability, as discussed in section IV.B, to provide clarity and transparency for prescribers.

We also recommend that the guidance explain that FDA's determination of interchangeability reflects its judgment that an interchangeable biosimilar product may be substituted only for the reference product—not another interchangeable product or biosimilar. Once multiple interchangeable products have been approved for a single reference product, there is risk that stakeholders will treat them as interchangeable with each other, even though they have only been shown interchangeable with the reference product. This risk is particularly acute given the extensive experience many physicians, patients, and pharmacists have with generic drugs that are substitutable with one another. Individual interchangeable products could have greater differences in structure, container closure system, and other attributes from each other than from the reference product. Moreover, two interchangeable products likely will not have been evaluated to determine if alternating or switching between them induces an immunogenic response.[11] Consequently, not only might multiple interchangeable products not meet the statutory standard of interchangeability with respect to one another, but switching among them may present the risk of additional or different immunogenicity issues than would result from switching between the reference product and a particular interchangeable product. The guidance should address these important issues regarding the implications of an interchangeability determination.

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[9] *See id*. § 351(i)(3); *see* PhRMA 2010 Comments, at 15-16 ("FDA should also issue a policy statement that unless it has deemed a biosimilar interchangeable with a prescribed product, that biosimilar should not be substituted for the prescribed product without the express consent of the prescribing physician.").

[10] *See* FDA, *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm (last visited May 18, 2017).

[11] *See* Draft Guidance, at 16 ("[W]ith switching, multiple exposures to each product can prime the immune system to recognize subtle differences in structural features between products, and the overall immune response could be increased under these conditions.").

Additionally, the guidance should clarify the relationship between the interchangeability standard under section 351(k)(4) of the PHSA and the therapeutic equivalence standard for drugs approved under section 505 of the FDCA. The standards are different, even though both are intended to determine whether two products are substitutable.[12] For example, to be therapeutic equivalents, drug products must be pharmaceutical equivalents, among other things,[13] whereas an interchangeability determination under section 351(k)(4) does not necessitate a showing of pharmaceutical equivalence. Indeed, it would be difficult, if not impossible, for virtually any follow-on biologic to satisfy this requirement with respect to its reference product; one key requirement for pharmaceutical equivalence is that drug products must share the "identical active drug ingredient."[14] As FDA has recognized, however, "[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."[15] Thus, therapeutic equivalence and interchangeability are not synonymous. Clarification of this point would help the health care community understand why biologics are treated differently from small-molecule drug products.

Accordingly, the guidance should expressly state that the showings needed to establish interchangeability and therapeutic equivalence are different. This clarification is particularly important because a new drug application (NDA) for a biological product will be deemed to be a license under section 351 of the PHSA on March 23, 2020, at which time these biological products will become subject to the interchangeability provisions of the PHSA and the recommendations in the guidance.[16] Because the statutory standard for interchangeability differs from the definition of therapeutic equivalence, a product that has received an "A" therapeutic equivalence rating and is subject to this transition provision will not necessarily have met the standard for interchangeability as of the transition date.[17]

The guidance also should clarify that, until March 23, 2020, the Agency will not accept or approve a section 351(k) application for a proposed interchangeable product that references a transition biological product. The PHSA mandates this approach, because it provides that FDA

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[12] *Compare* PHSA § 351(i)(3) (defining "interchangeable" to mean that the product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product") *with Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), at vii (37th ed. 2017) (in general, "FDA believes that 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").

[13] *See* Orange Book, at vii.

[14] 21 C.F.R. § 314.3(b) (definition of "Pharmaceutical equivalents"); *see also* Orange Book, at vii.

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

[16] *See* BPCIA § 7002(e)(4); FDA, Draft Guidance for Industry, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*, at 1 (Mar. 2016) (Transition Biological Products Draft Guidance).

[17] For example, certain chorionic gonadotropin products are transition biological products that have "AP" therapeutic equivalence ratings. *See* Orange Book (entry for "gonadotropin, chorionic"); Transition Biological Products Draft Guidance, at 10 (identifying chorionic gonadotropin products as transition biological products).

must determine the interchangeability of a proposed product to a "reference product."[18] Before March 23, 2020, a transition biological product cannot serve as a reference product because it does not meet an essential element of the definition of a reference product—i.e., it is not "licensed under [PHSA §351](a)."[19] Further, FDA may make an interchangeability determination only "[u]pon review of an application submitted under [PHSA § 351(k)] or any supplement to such application."[20] Until the transition date, an application for a follow-on transition biological product cannot be submitted under section 351(k), because there will be no "reference product" for that application. PhRMA believes that these revisions will provide much-needed clarity to the sponsors of transition biological products.

II. The Guidance Should Further Clarify the Data and Information Needed To Establish Interchangeability.

A. FDA Should Clarify When Interchangeability Could Be Established in an Original Section 351(k) Application, When Postmarket Data Are Needed, and What Kind of Postmarket Data Are Recommended.

The draft guidance suggests that an applicant may obtain a determination of interchangeability for a product that was not initially licensed as a non-interchangeable biosimilar product. For example, the draft guidance suggests that "an integrated, two-part study design may be appropriate" to demonstrate both biosimilarity and interchangeability.[21] This proposed approach appears to depart from a May 2015 draft guidance that states "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment."[22] We ask that FDA clarify whether it now believes that it is scientifically feasible for an applicant to demonstrate interchangeability in an original application and, if so, the conditions that would allow an applicant to make that demonstration.

For two reasons, postmarketing data in a large patient population generally are necessary to assessing whether a biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and whether alternating or switching between the proposed product and reference product increases risk in terms of safety or diminished efficacy. First, current analytical techniques do not have complete clinical predictive

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[18] *See* PHSA § 351(k)(4).

[19] PHSA § 351(i)(4); *see also* Letter from Janet Woodcock, M.D., FDA, to Sarfaraz K. Niazi, Ph.D., Therapeutic Proteins, Inc., re: Docket No. FDA-2009-P-0004-0004, at 4 (Feb. 24, 2012) ("[T]he availability of an abbreviated approval pathway for a protein or peptide product that seeks to rely, to some extent, upon a previously approved product is governed by the statutory authority under which the previous product was approved or licensed as well as by scientific considerations.").

[20] PHSA § 351(k)(4).

[21] Draft Guidance, at 12.

[22] FDA, Draft Guidance for Industry, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at 6-7 (May 2015).

value, particularly with respect to predicting immunogenicity.[23] Second, as FDA has recognized, "[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."[24] Use under real-world conditions is needed to detect any rare immunogenic events that could be caused by switching or alternating or identify patient populations or circumstances where switching presents greater concern. In particular, PhRMA believes that postmarketing data generally are necessary to determine interchangeability of more complex biological products, such as those with the potential for immunogenicity-related risks, diverse indications spanning multiple therapeutic areas, and/or multiple mechanisms of action.

PhRMA also requests that the guidance describe (1) the type of postmarketing clinical study, other than a switching study or studies, that may be necessary to support a demonstration of interchangeability or to address residual uncertainty; and (2) when such a study is warranted. This information would help clarify the statement in the draft guidance that "there may be situations where a postmarketing study, in addition to postmarketing surveillance data, from the licensed biosimilar product may be needed to address residual uncertainty regarding a demonstration of interchangeability."[25]

PhRMA recommends that postmarketing data be sufficiently robust to identify safety and efficacy signals that warrant further investigation in a switching study and generally include more than passive surveillance of safety events. Postmarket data to support interchangeability should be collected using the U.S.-licensed reference product as the comparator unless the potential for "subtle differences between the U.S.-licensed reference product and the non-U.S.-licensed product" can be ruled out.[26]

B. FDA Should Consider Additional Statistical Approaches for Analyzing PK Data.

The draft guidance recommends that applicants provide PK data from switching studies that meet the standard limits for average bioequivalence (BE) used in the generic drug context.[27] PhRMA suggests that FDA consider recommending additional statistical approaches—such as those that take into consideration subject-by-formulation variability (e.g., individual BE)—to satisfy the statutory requirement that an interchangeable product "can be expected to produce

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[23] *See, e.g.*, Scientific Considerations Guidance, at 16; PhRMA 2010 Comments, at 11 ("Analytical data alone would be insufficient to ensure that a biosimilar substituted without the intervention of a healthcare professional would generate no difference in clinical result.").

[24] Scientific Considerations Guidance, at 22.

[25] Draft Guidance, at 8. This topic should be included in section VI, "Data and Information Needed To Support a Demonstration of Interchangeability." *See id*. at 9-15.

[26] *See id.* at 16.

[27] According to the draft guidance, "[t]he log-transformed AUC_{tau} and C_{max} data should be statistically analyzed using an analysis of the variance. The 90% confidence interval for the geometric mean ratio of AUC_{tau} and C_{max} between the proposed interchangeable product and the reference product should be within 80-125%." Draft Guidance, at 12; *see also* FDA, Guidance for Industry, *Statistical Approaches to Establishing Bioequivalence*, at 2 (Jan. 2001) (BE Statistical Approaches Guidance).

the same clinical result as the reference product in any given patient."[28] These assessments could be done as part of the switching study.

As FDA has explained, "[t]he average BE method does not assess a subject-by-formulation interaction variance, that is, the variation in the average [test] and [reference] difference among individuals."[29] Accordingly, average BE might not detect that a small percentage of patients have PK differences between the test and reference products and therefore, might experience safety or efficacy differences between a proposed interchangeable product and the reference product. Failures in subsets of patients are not consistent with the unique, patient-focused, "any given patient" standard in section 351(k)(4). By contrast, alternative statistical approaches, such as individual BE, can "assess within-subject variability for the [test] and [reference] products, as well as the subject-by-formulation interaction."[30] Such alternative approaches therefore show whether "any given patient" is experiencing comparable exposure when switched. Thus, FDA should consider recommending other statistical approaches that assess subject-by-formulation interaction variance as part of the switching study to demonstrate that the "any given patient" requirement has been met.

C. FDA Should Provide Further Guidance on the Design of Switching Studies.

PhRMA requests further guidance on several open issues relating to the design of switching studies.

First, the draft guidance recommends that "[a] switching study or studies should evaluate changes in treatment that result in *two or more* alternating exposures (switch intervals) to the proposed interchangeable product and to the reference product."[31] We ask that FDA explain the factors that will determine the appropriate number of exposure periods. Second, the final guidance should clarify whether the design and data analysis considerations discussed in connection with a dedicated switching study design (*see* section VI.A.2.a) also apply to an integrated study design (*see* section VI.A.2.b).[32] Additionally, we suggest that the recommended structure of a switching study be illustrated through a graphic.

Moreover, to ensure that switching studies capture data relevant to the statutory standard for interchangeability, such studies generally should include a robust assessment of efficacy and immunogenicity.[33] These data generally are needed to demonstrate 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."[34]

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[28] PHSA § 351(k)(4)(A)(ii).

[29] BE Statistical Approaches Guidance, at 3.

[30] *Id.*

[31] Draft Guidance, at 9 (emphasis added).

[32] *See id.* at 10-12.

[33] *Id.* at 10.

[34] PHSA § 351(k)(4)(B).

Some efficacy differences resulting from structural differences between a proposed interchangeable product and reference product might not be reflected in PK differences and therefore, could be detected only through a comparative effectiveness assessment.[35] Similarly, some immunogenicity differences are not reflected in PK differences, as FDA previously recognized in recommending that a sponsor conduct a clinical immunogenicity assessment in addition to comparative PK and PD studies.[36] As FDA explained, a change in PK is only one possible effect of a clinically relevant immune response:

> Immune responses may affect both the safety and effectiveness of the drug product by, for example, altering PK, inducing anaphylaxis, or promoting development of neutralizing antibodies that neutralize the product as well as its endogenous protein counterpart.[37]

Because PK and PD endpoints might not capture all potential differences between the reference product and a proposed interchangeable product that may have clinical relevance, switching studies generally should include robust efficacy and immunogenicity assessments.[38]

D. FDA Should Clarify the Type of Scientific Justification That Would Support the Use of a Non-U.S. Licensed Comparator in Switching Studies.

PhRMA generally agrees with FDA's recommendation that "sponsors [should] use a U.S.-licensed reference product in a switching study or studies" due to the potential for "subtle differences between the U.S.-licensed reference product and the non-U.S.-licensed comparator product" and the resulting uncertainty as to the relevance of the results from a switching study conducted using a non-U.S.-licensed comparator product.[39] The draft guidance states, however, that an applicant may submit a "proposal to provide adequate scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator product to support a demonstration of interchangeability."[40] We ask that FDA clarify that a U.S.-licensed reference product should be used in switching studies unless the potential for subtle differences from the foreign comparator can be ruled out.[41]

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[35] *See* Liu L., 2015, *Antibody Glycosylation and Its Impact on the Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies and Fc-Fusion Proteins*, J Pharm Sci, 104:1866–1884.

[36] Scientific Considerations Guidance, at 14.

[37] *Id*. at 16.

[38] Although the draft guidance notes that "[i]n addition to PK and PD parameters, a switching study or studies would also be expected to assess immunogenicity and safety," as well as effectiveness, Draft Guidance, at 10 & 12, it does not make clear FDA's expectations as to the robustness of such data. Rather, the draft guidance recommends that "[s]afety, immunogenicity, and efficacy should be descriptively analyzed as secondary endpoints." *Id*. at 12.

[39] *Id*. at 16.

[40] *Id*.

[41] Indeed, in a final guidance issued in April 2015, FDA concluded that "[a]t this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S. licensed product would be an adequate basis to support the additional criteria required for a determination of interchangeability with the U.S.-
(continued...)

E. FDA Should Clarify the Meaning of "Fingerprint-Like Characterization."

In the draft guidance and in previous guidance documents, FDA has described a "fingerprint-like characterization" as an analytical approach that may be used to support a demonstration of biosimilarity or interchangeability, but the meaning of that phrase remains unclear.[42] In other guidance documents, FDA has referred to a "fingerprint-like analysis algorithm that covers a large number of additional product attributes and their combinations with high sensitivity using orthogonal methods"[43] and has described "fingerprint-like analyses" as "the results of integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences."[44] Additionally, two guidance documents cite a publication by FDA authors that describes "a 'fingerprint'-like identification of very similar patterns in two different products" analogous to the strategy used to obtain approval of generic enoxaparin.[45] We request that FDA further clarify the meaning of "fingerprint-like characterization" and how a sponsor may achieve it in order for PhRMA and other stakeholders to fully evaluate and comment on this concept.

F. FDA's Assessment of a Proposed Presentation Should Take Account of the Potential Risks of Use-Related Error in Patients Who Have Substantial Experience with the Reference Product.

PhRMA agrees with FDA that sponsors should conduct a threshold analysis of the proposed interchangeable product and the reference product to identify and evaluate differences in the design of presentations and should provide appropriate data (from comparative use human factors studies or additional studies) to support interchangeability where the threshold analysis shows that a design difference may not be minor.[46] PhRMA also agrees that patients and caregivers "may be at increased risk for a use-related error that may impact their ability to appropriately use these products" as compared with health care providers.[47] FDA should consider whether patients with significant experience with the reference product presentation may be at an increased risk of confusion and use-related errors upon substitution of a presentation with design differences without training or other intervention. As FDA recognized

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licensed reference product." FDA, Guidance for Industry, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at 10 (Apr. 2015) (Q&A Guidance).

[42] Draft Guidance, at 6.

[43] FDA, Guidance for Industry, *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*, at 8 (Apr. 2015).

[44] FDA, Guidance for Industry, *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*, at 6 (Dec. 2016).

[45] Kozlowski S et al., 2011, Developing the Nation's Biosimilars Program, N Engl J Med, 365:385-388.

[46] Draft Guidance, at 18-23. The draft guidance states that the threshold analyses "may be used in the development of the proposed presentation to minimize differences between the proposed interchangeable product and the reference product . . . ." *Id.* at 18. FDA should clarify such differences to be minimized do not include trademarks or logos, as those are not attributes that affect the user interface. Therefore, differences in these attributes would not compromise the safe use of the presentation.

[47] *Id.* at 19-20.

in its draft guidance on human factors studies for combination products, the "experience of individual [lay] users with similar products or products under development may vary widely," so "there may be distinct subgroups that should be considered in the use-related risk analysis."[48] PhRMA believes that the interchangeability guidance should provide that FDA will evaluate the threshold analyses and determine data requirements stemming from presentation differences (e.g., the need for comparative use human factors studies) with due consideration of the potential increased risk of use errors in patients who have long used the reference product presentation. FDA also should address labeling issues associated with interchangeability, including with respect to device-related information and training by prescribers.

III. PhRMA Recommends that FDA Strengthen the Draft Guidance Content on Demonstrating Interchangeability for All Reference Product Conditions of Use.

A. The Sponsor of a Proposed Interchangeable Product Is Required To Demonstrate Interchangeability for All Reference Product Conditions of Use Even If Approval Is Not Sought for All Such Conditions of Use.

PhRMA agrees that it is appropriate for the sponsor of a proposed interchangeable product to demonstrate interchangeability in all of the reference product's approved conditions of use.[49] We also agree that clinical trials need not be conducted in each of the reference product's approved conditions of use in order to demonstrate interchangeability for that condition of use.[50] Instead, the sponsor may provide "a scientific rationale to extrapolate data and information supporting a demonstration of interchangeability in an appropriate condition of use to the remaining conditions of use for which the reference product is licensed."[51] But whereas the draft guidance states that "FDA expects" sponsors to demonstrate interchangeability in all of the reference product's approved conditions of use, PhRMA requests that FDA expressly recognize that the PHSA requires sponsors to do so.

As noted, a sponsor seeking an interchangeability determination must demonstrate, among other things, that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient,"[52] and a determination of

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[48] FDA, Draft Guidance for Industry and FDA Staff, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*, at 8 (Feb. 2016). We ask that FDA clarify the relationship between the cited human factors draft guidance and the recommendations in section VIII (Considerations for Developing Presentations for Proposed Interchangeable Products) of the draft guidance.

[49] Draft Guidance, at 3; *see* PhRMA 2010 Comments, at 10-11. For consistency with this principle, we recommend that FDA revise lines 525-528 of the draft guidance, which currently provide that "[t]he sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed *and for which licensure as an interchangeable product is sought*." (emphasis added). The italicized language should be replaced with "at the time of the request for designation regardless of whether licensure for that condition of use is sought."

[50] Draft Guidance, at 3-4.

[51] *Id*. at 3.

[52] PHSA § 351(k)(4)(A)(ii).

interchangeability represents FDA's judgment that the proposed product may be substituted for the reference product without the intervention of the prescriber.[53] If the reference product has been approved for multiple conditions of use, a pharmacist aiming to determine whether to substitute for the reference product is unlikely to know the condition of use for which the reference product was prescribed because a prescription likely would not include that information. Even if the pharmacist had that knowledge, the Purple Book apparently will list interchangeability determinations by product, not by condition of use. For these reasons and based on experience with generic drug substitution, pharmacies likely will substitute interchangeable products for the reference product without regard to the condition of use for which the reference product was prescribed.

Consequently, application of the "any given patient" standard must take into consideration patients who receive the interchangeable product for any of the reference product's approved conditions of use. Indeed, if interchangeability were not shown for a reference product condition of use, the proposed interchangeable product would fail to satisfy the requirement that it "can be expected to produce the same clinical result as the reference product in any given patient" for that condition of use.[54] To satisfy section 351(k)(4)(A)(ii) of the PHSA, then, the sponsor must demonstrate interchangeability for all of the reference product's approved conditions of use. PhRMA asks that FDA revise the guidance to clarify that this is a statutory requirement. This approach is in the best interests of patients, as any other approach would create the risk of inappropriate substitution (potentially resulting in safety or efficacy issues) in cases where FDA has determined that the proposed product is interchangeable with the reference product, but not for the prescribed condition of use.

Moreover, although biosimilar products may be approved for a subset of presentations approved for the reference product,[55] FDA should consider whether it must approve an interchangeable product for all reference product presentations, given that an interchangeable product "may be substituted for the reference product without the intervention of the [prescriber]."[56]

B. The Sponsor Should Justify Interchangeability for Conditions of Use Later Approved for the Reference Product.

As requested in the *Federal Register* notice accompanying the draft guidance, PhRMA offers its thoughts on "[h]ow, if at all, [FDA should] consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed[.]"[57] PhRMA believes that if a new condition of use is approved for the reference product following FDA's initial determination of interchangeability, the Agency should require the sponsor of the interchangeable product to provide scientific justification for interchangeability as to the newly approved condition of use in order to maintain the product's designation as an interchangeable product. Such justification could be submitted in a supplemental biologics license application if

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[53] PHSA § 351(i)(3).

[54] *Id*. § 351(k)(4)(A)(ii).

[55] *See* Q&A Guidance, at 7.

[56] PHSA § 351(i)(3).

[57] 82 Fed. Reg. at 5580.

the sponsor of the interchangeable product were to seek approval for the new condition of use, or through some other form if, for example, the sponsor did not seek to add the new condition of use to the labeling of the interchangeable product (e.g., due to orphan drug exclusivity). We anticipate that sponsors of interchangeable products rarely would encounter scientific difficulties in providing such justification.

IV. FDA Should Provide Guidance on the Naming and Labeling of Interchangeable Products.

In FDA's prior guidance documents on biosimilar naming and labeling, the Agency deferred addressing issues relating to the naming and labeling of interchangeable products.[58] Given the release of the draft guidance, PhRMA asks that FDA now provide guidance on naming and labeling issues for interchangeable products. PhRMA previously expressed its views on these issues through comments on FDA's draft guidance documents on naming and labeling, and in a citizen petition addressing biosimilar labeling that PhRMA jointly submitted with the Biotechnology Industry Organization (BIO).[59] PhRMA summarizes its positions here.

A. The Nonproprietary Names of Interchangeable Products Should Include Unique Suffixes.

PhRMA urges FDA to include unique suffixes in the nonproprietary names of interchangeable products to promote safe use and effective pharmacovigilance. Those interests led FDA to adopt a naming convention that provides for distinguishable nonproprietary names for biological products.[60] Under the final guidance on naming, the nonproprietary names for a reference product and a corresponding biosimilar product will share the same "core name"—generally the United States Adopted Name (USAN)—but will have different suffixes that are devoid of meaning, composed of four lowercase letters, and attached to the core name with a hyphen.[61]

Like other biosimilar products, interchangeable products need to be distinguishable from the reference product and from each other in the interests of safe use and accurate pharmacovigilance. If multiple interchangeable versions of a single reference product were assigned the same suffix without an FDA determination that they are interchangeable to each other, there might be inadvertent substitution among these products. Moreover, assigning a unique suffix to each product would help identify the product associated with a given adverse event. Even extensive interchangeability studies might not detect extremely rare, product-specific immunogenicity issues, new signals of which may emerge in the postmarketing setting. As FDA previously explained, "surveillance systems [must] be able to detect safety signals

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[58] *See* FDA, Guidance for Industry, *Nonproprietary Naming of Biological Products*, at 1 (Jan. 2017) (Nonproprietary Naming Guidance) ("FDA is continuing to consider the appropriate suffix format for *interchangeable products*.") (emphasis in original); FDA, Draft Guidance for Industry, *Labeling for Biosimilar Products*, at 12 (Mar. 2016) ("Any specific recommendations for labeling for interchangeable biological products, including any interchangeability statement . . . will be provided in future guidance.").

[59] *See* PhRMA, Comment, Docket No. FDA-2016-D-0643-0042, at 6-8 (July 26, 2016); PhRMA & BIO, Citizen Petition, Docket No. FDA-2015-P-5022-0001, at 5-6 (Dec. 22, 2015); PhRMA, Comment, Docket No. FDA-2013-D-1543-0149, at 11-12 (Oct. 27, 2015).

[60] *See* Nonproprietary Naming Guidance, at 4-6.

[61] *Id*. at 7-8.

throughout the lifecycle of a product"[62]—not just until a biosimilar is deemed interchangeable with its reference product. For these reasons, PhRMA recommends that for interchangeable products, FDA should follow its general naming convention for biological products: the nonproprietary name of each interchangeable biosimilar product should bear a suffix identifier that is distinct from the suffix used for the reference product and for other interchangeable products.

B. Biosimilar Labeling Should Include a Statement Regarding Interchangeability.

Biosimilar labeling should include a statement regarding whether or not FDA has made a determination of interchangeability with the reference product and that includes any such finding. This interchangeability statement should appear in conjunction with the biosimilarity statement that FDA has proposed for inclusion in the labeling.[63] Also, in order to prevent confusion, FDA's proposed footnote defining biosimilarity should be accompanied by the statutory definition of interchangeability.[64]

Such a statement in biosimilar labeling is essential to prevent inadvertent substitution: without such a statement, prescribers may reach the mistaken conclusion that substitution is appropriate when FDA has made no interchangeability determination. Indeed, FDA previously recognized that information about whether FDA has or has not determined that a product is interchangeable is "necessary for a health professional to make prescribing decisions."[65] Moreover, in a survey of physicians, 79 percent responded that they consider it important for biosimilar labeling to "clearly indicate a biosimilar is or is not interchangeable."[66] The interchangeability statement and the statutory definition of interchangeability should be placed adjacent to the proposed biosimilarity statement and footnote defining biosimilarity, in order to help clarify the distinction between biosimilarity and interchangeability.

V. Other Comments

PhRMA recommends that the guidance address the following issue regarding exclusivity for a first interchangeable biological product as described in section 351(k)(6) of the PHSA. The guidance should clarify how FDA will determine the sequence of approval of interchangeable

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[62] 80 Fed. Reg. at 52,226 (emphasis added).

[63] *See* FDA, Draft Guidance for Industry, *Labeling for Biosimilar Products*, at 8-9 (Mar. 2016).

[64] *See id*. at 9.

[65] *See* FDA, Draft Guidance for Industry, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 21 (Feb. 2012) ("Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that: . . . This product (has or has not) been determined to be interchangeable with the reference product."). FDA later finalized this guidance without the content on labeling. *See* Scientific Considerations Guidance. In a letter to Senator Alexander, FDA stated: "FDA did not address labeling issues in [the final guidance] because it was considered outside the scope of that guidance." Letter from Thomas A. Kraus, Associate Commissioner for Legislation, FDA, to Hon. Lamar Alexander, Chairman, Committee on Health, Education, Labor & Pensions, U.S. Senate, at 3 (June 22, 2015).

[66] Kevin Olson, ASBM Labeling Survey (Feb. 2015), https://safebiologics.org/wp-content/uploads/2016/04/February-2015-Labeling-Report.pdf, at slide 19.

products for purposes of implementing exclusivity, where multiple applications for proposed interchangeable products for the same reference product are submitted on the same day and are subject to the same review timeline. For instance, on March 23, 2020, transition biological products will become potential reference products for the first time, and multiple applications for proposed interchangeable products may be submitted for any given transition biological product on that date.

With respect to question 1 in the Notice of Availability for the draft guidance, which regards the regulation of post-approval manufacturing changes for interchangeable products, PhRMA acknowledges that this question raises an important issue.[67] PhRMA asks that FDA develop a policy to address this issue and provide the opportunity for stakeholder input on the Agency's proposed approach.

VI. Conclusion

PhRMA appreciates the Agency's efforts to develop its policy on interchangeable products through the public guidance process. PhRMA looks forward to continued collaboration with FDA on the Agency's implementation of the BPCIA. We would welcome the opportunity to discuss these comments further.

Respectfully submitted,

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[67] 82 Fed. Reg. at 5580.