PhRMA

April 16, 2012

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

Re: Docket No. FDA-2011-D-0605: Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; 77 Fed. Reg. 8883 (Feb. 15, 2012)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to FDA's issuance of draft guidance for industry entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" ("*Scientific Considerations* draft guidance" or the "draft guidance").[1] PhRMA is a voluntary, nonprofit association that represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. In 2011, PhRMA members invested nearly $50 billion to develop new medicines.

PhRMA supported enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA), believing that the statute struck an appropriate balance between protecting and encouraging innovation, on the one hand, and timely market entry of lower cost biosimilar products, on the other hand. We were pleased to participate in, and to offer supplementary written comments to, FDA's Part 15 hearing in 2010 to begin implementation of the BPCIA. Given the complexity of the scientific, regulatory, and policy issues related to developing, manufacturing, and approving biosimilars, we applaud FDA's decision to seek public input by issuing this draft guidance, as well as two additional draft guidances, on implementation of the BPCIA and the considerations relevant to establishing biosimilarity. We are pleased to offer the following comments on the draft guidance, and we hope that FDA will continue to seek stakeholder input openly and transparently as it implements the BPCIA.

I. Introduction and General Comments

FDA's approach to demonstrating biosimilarity should be guided by the foundational premise of the BPCIA: that, to protect patient safety, an abbreviated licensure pathway is appropriate only for those biological products that have been demonstrated to be highly similar to, and devoid of any clinically meaningful differences in safety, purity, and

[1] 77 Fed. Reg. 8883 (Feb. 15, 2012).

potency from, the reference product. Biologics are highly complex products, and even small changes may have unintended clinical consequences that may be difficult to anticipate in the absence of extensive manufacturing experience with the proposed biosimilar product. For the statute to function as intended to protect patients, it is thus critical for FDA to require that the abbreviated approach taken by each biosimilar applicant — in establishing biosimilarity to a reference product, *rather than* demonstrating safety and effectiveness de novo in a full application — be fully scientifically justified. Accordingly, PhRMA recommends that FDA's implementation of biosimilarity standards, including the development of guidances, be consistent with the following principles:

- **Maximize Public Participation and Transparency**. Establishing biosimilarity standards — both at a general level and on a product class by product class basis — in a transparent and participatory manner will help to ensure the safety, efficacy, and timely market entry of biosimilars for patients. Opportunities for public comment permit reference product sponsors — who have unique insight into biologic product characteristics and manufacturing processes — to provide input into the standards necessary to ensure safe and effective biosimilars. A transparent public process also allows other stakeholders to provide input with respect to both scientific standards and pragmatic issues raised by biosimilar biological products, and it should promote better public appreciation of the process by which biosimilars are approved, thereby facilitating physician education and patient understanding of biosimilar products. Although drafting guidance (including on a product class basis) will require an investment of time and resources, the agency can carefully prioritize issues and product classes (for example, by focusing on product classes as to which it has received multiple requests for guidance from individual applicants) to minimize unnecessary burden. PhRMA therefore recommends that FDA continue to utilize a public process to enable FDA and the scientific community to resolve important issues early and cooperatively, which may help to ensure that the agency's final conclusions achieve widespread acceptance.

- **Minimize Controllable Differences.** The basic purpose of the BPCIA is to establish an approval pathway for biological products that are highly similar to proven therapies. To protect patients, the statute imposes a scientifically rigorous standard that each product must be highly similar to its reference product and not meaningfully different from a clinical perspective. Intentionally introducing differences to the molecule or the finished product will increase the level of uncertainty regarding the proposed biosimilar's similarity to the reference product, potentially increasing the risk of unintended or unanticipated clinically meaningful differences. To ensure that unintended or unanticipated differences in quality, safety or efficacy do not evade premarket detection, additional analytical, preclinical, and clinical studies may be necessary to adequately demonstrate that the biosimilar is highly similar to the reference product. Both public health considerations and statutory considerations therefore counsel that FDA guidance should recommend that applicants minimize controllable process and design differences to the extent feasible and that they provide scientific justification for changes to controllable elements of the proposed biosimilar product, recognizing that the feasibility of an abbreviated development

program for a proposed biosimilar is diminished by the intentional introduction of differences.

- **Recognize the Limits of State-of-the-Art Technology.** Comparative analytical characterization forms the foundation of the biosimilarity assessment, but even state-of-the-art analytical technology may not identify all differences between a proposed biosimilar and the reference product. Because the statutory standard for biosimilarity rests in the negative — in establishing the *absence* of clinically meaningful differences — recognizing an analytical program's limitations is equally important as, if not more important than, recognizing its strengths. A thorough understanding of each analytical method's limitations will be critical to applicants' successful identification of residual uncertainties and, in turn, to the design of appropriate preclinical and clinical studies to resolve these uncertainties.

II. Comments by Topic

A. Stepwise Approach

PhRMA endorses the draft guidance's recommendation that applicants take a "stepwise approach" to demonstrating biosimilarity.[2] As the draft guidance recognizes, this process should begin with comparative molecular evaluations of physicochemical and functional properties, generally be followed by preclinical animal studies, and conclude with clinical testing. The draft guidance further directs the sponsor to assess, at each step of the process, the extent to which residual uncertainty about biosimilarity of the proposed biosimilar to the reference product remains and to design subsequent testing to further investigate and seek to resolve these uncertainties. PhRMA supports this approach, although we urge caution with respect to "residual uncertainty," particularly when considering the potential impact of these uncertainties on clinical safety and efficacy. The reliability of analytical findings is inherently limited by both study design and the sensitivity and specificity of the methods employed, and even with state-of-the-art technology PhRMA does not believe that it is possible at this time to identify all differences between a proposed biosimilar and the reference product. Assurance that all residual uncertainties have been identified and addressed presupposes that an applicant recognizes the necessary questions to ask, designs the appropriate studies to resolve these questions, identifies the limitations of its analytical methodology, and is aware of the points at which product dissimilarities might arise. Given the complexity and heterogeneity of biologics, and the fact that applicants may lack robust manufacturing experience with a particular biologic or a proposed biosimilar product, this may not always be the case. Accordingly, PhRMA believes that the final guidance should recommend that a stepwise approach to demonstrating biosimilarity include at least one clinical study to establish that the proposed biosimilar product does not possess clinically meaningful differences in safety, purity, or potency from its reference product.

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[2] FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," *Draft* (Feb. 2012), at 2 (hereafter the "*Scientific Considerations* Draft Guidance").

B. Transparent, Public Process

As FDA continues to implement the BPCIA and particularly as it develops the scientific standards governing biosimilarity, PhRMA encourages the agency to employ a transparent and participatory process with opportunities for public comment on future scientific and procedural guidances. Drawing on the experience and knowledge offered by stakeholders, including innovators, healthcare professionals, and the general scientific community, will help to ensure the safety, efficacy, and timely market entry of biosimilars. Innovators in particular possess intimate knowledge of and longstanding manufacturing experience with these products and can provide valuable insight to FDA about issues that should be considered when establishing or evaluating biosimilarity. Indeed, for this reason, PhRMA urges the agency to solicit public comment on, and issue guidances that address, analytical, preclinical, and clinical issues for individual product classes. Although class guidances would be unlikely to address all nuances of product development or issues specific to individual proposed products, an open process for each product class would give the agency more information relevant to ensuring the safety and efficacy of biosimilars in that class, could conserve agency resources if timed to facilitate public input when questions relating to particular product types begin to proliferate, and would contribute to transparency and predictability more generally.

C. Relationship Between Biosimilarity & Comparability Demonstrations

PhRMA appreciates FDA's recognition that biosimilarity demonstrations between proposed biosimilar and reference products are distinct from, and typically more complex than, comparability demonstrations by manufacturers of their own products. Biological products are sensitive to their manufacturing processes, and even seemingly minor modifications may alter a product's clinical profile. As the draft guidance helpfully acknowledges, a manufacturer that modifies its own process draws on its extensive — and typically proprietary — knowledge about both the product and the existing process. This wealth of experience enables manufacturers to better anticipate the effect of process parameter changes, especially where the potential for clinical implications exists. In contrast, a biosimilar manufacturer is unlikely to know the details of the reference product's manufacture, will in any case use a different manufacturing process, and may lack a comparably extensive experience with that process. Standards for comparability demonstrations may therefore be relevant to a demonstration of biosimilarity, but are insufficient standing alone.

D. Definition of Biological Product

As amended by the BPCIA, section 351(i) of the PHSA now states that a biological product includes any "protein (except any chemically synthesized polypeptide)." The statute does not further define these terms, and the draft guidance offers FDA's first public articulation of definitions for "protein" and "chemically synthesized polypeptide." Under the draft guidance (*Attachment: Terminology,* page 22), a "protein" would include any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. A "chemically synthesized polypeptide," which would be carved out from regulation as a biological product, would constitute any alpha amino acid polymer that is made entirely by chemical synthesis and that is fewer than 100 amino acids in size.

Establishing definitions of "protein" and "chemically synthesized polypeptide" is integral to BPCIA implementation, and PhRMA appreciates the fact that FDA has proposed definitions for public comment. FDA has not provided a scientific basis or justification for the definitions as they currently stand, however, and we strongly urge the agency to revisit these terms in the final guidance and to incorporate considerations of manufacturing method and molecule structure into the definitions of "protein" and "chemically synthesized polypeptide." PhRMA recognizes that distinguishing proteins from peptides based solely on size — creating a "bright-line" test of 40 amino acids — may be a simpler standard to administer. But PhRMA believes the agency must take an approach that is administratively workable, scientifically defensible, and appropriately reflective of factors that influence the complexity of molecules (such as the structure and function of the molecule and the method of manufacture). PhRMA is not aware of scientific consensus that would support the proposed basis for differentiating between "polypeptide," "protein," and "peptide," and we note that a 40-amino acid polypeptide may not be qualitatively different from a 39-amino acid molecule. Yet, the molecules would be regulated wholly differently under the statute. The 100-amino acid upper limit for chemically synthesized polypeptides, too, is unlikely to distinguish meaningfully between products in terms of function, quality, or other relevant attributes.

PhRMA therefore urges the agency to adopt a more nuanced and functional approach to these definitions. Specifically, PhRMA proposes that the final guidance should state that a polypeptide should be regulated under the PHSA as a protein if it is an alpha amino acid polymer with a specific defined sequence that exists in a stable multi-dimensional conformation and is manufactured by a process that utilizes a biological system in addition to chemical synthesis. The use of living cells or source material that is otherwise biological in nature would be the primary factors FDA should look to in determining that a product was manufactured biologically. A "chemically synthesized polypeptide," which would be regulated under the FDCA, should be any linear chain of alpha amino acids that is made entirely by chemical synthesis and does not depend on higher order structure (secondary and above) for its function.

E. Products Not Currently Suitable for the 351(k) Pathway

Section 351(k)(8)(E) of the PHSA permits FDA to state in guidance that — based on current science and experience — a particular product or product class (excluding recombinant proteins) is not suitable for approval via an abbreviated licensure pathway. In its October 2010 *Federal Register* notice, FDA asked for comment on the scientific and technical factors that should be considered when implementing this provision. The draft guidance (Section VII.A. *Structural Analysis*, lines 358-360) notes that if a *particular* reference product cannot be adequately characterized, applicants should "consult" with FDA about whether a 351(k) application is appropriate.[3] But it takes no position on particular product classes. PhRMA urges FDA to affirm the statement in the *Quality Considerations* draft guidance (Section III. *Scope*, lines 164-168) by clarifying in the *Scientific Considerations* final guidance that *both* the reference product and proposed biosimilar product should be adequately characterized with state-

[3] *Id.* at 10.

of-the-art technology for an application for the proposed biosimilar product to be appropriate for submission under section 351(k) of the PHS Act.

PhRMA recommends that FDA strengthen the comment made in the draft guidance. Robust, comparative analytical characterization is foundational to the biosimilarity assessment. The stepwise approach outlined in the draft guidance is premised upon the principle that the preclinical and clinical testing steps may be designed (and proceed) only once a robust analytical program has in fact accurately identified, to the extent possible, uncertainties regarding the biosimilarity of the two products. Consequently, although PhRMA generally support the notion of consultation with FDA where characterization of either the reference product or the biosimilar presents challenges, we cannot envision a scenario in which the 351(k) pathway would remain appropriate unless both the proposed biosimilar and reference biologic were well-characterized. PhRMA therefore suggests that the agency more plainly state in the final guidance that both the proposed biosimilar and the reference product should be well-characterized by the biosimilar applicant to permit use of the 351(k) pathway.

Separately, however, PhRMA encourages FDA to describe additional factors that may affect the feasibility of abbreviated licensure and to identify product classes that are not currently suitable for the 351(k) pathway. Moreover, as the agency continues to assess the factors that may preclude approval of a product or class of products under an abbreviated pathway, we recommend that FDA primarily focus on the ability of current technology to characterize the quality attributes of the molecules at issue, to detect any differences between the molecules, and to demonstrate how these differences may affect clinical outcomes.

In light of these considerations, PhRMA believes that vaccines and blood products should be licensed only on the basis of full applications under section 351(a) for the foreseeable future. While we recognize that the statute permits FDA to state preemptively in guidance only that *non-recombinant* vaccines and blood products cannot be the subject of 351(k) applications, it is our view that, at least for the foreseeable future, all vaccines and blood products will in fact need to be the subject of full applications. Blood products raise more complex product, process, and characterization issues than do other biologics. Establishing the absence of clinically meaningful differences between a proposed biosimilar and the reference blood product on the basis of an abbreviated premarket program could be challenging — and potentially unreliable — which could present risks to patient safety. Similarly, public health considerations counsel against the marketing of vaccines on the basis of abbreviated trials. The benefit/risk ratio is significantly different for vaccines than for other biological products, because vaccines are generally administered to healthy populations and are frequently administered to children. Other jurisdictions, including the EU and Japan, have also taken an extremely cautious approach to including vaccines in an abbreviated pathway.[4] And vaccines are excluded from the scope of the WHO guidelines on biosimilar products.[5]

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[4] *See, e.g.*, Japan, PFSB/ELD No. 0304007, Guidelines on the Quality, Safety and Efficacy Assurance of Follow-on Biologics 4 (2009) (stating that "conventional vaccines" are excluded from the scope of the biosimilar guidance); EMA Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products 6 (2005) ("Vaccines are complex

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F. Foreign Comparators

The BPCIA requires that a biosimilar product be compared to a "reference product," which is defined as "the *single* biological product *licensed under subsection (a)* against which a biological product is evaluated in an application submitted under subsection (k)."[6] The statute thus dictates that a proposed biosimilar be compared to only one reference product and that this single reference product be licensed by FDA under section 351(a).[7] This means that any comparative analytical, preclinical, and clinical studies required by FDA pursuant to section 351(k) must use the FDA-licensed product.

FDA defines an approved product to mean the specific product substance made by a specific manufacturer, as described in the application, which covers such details as "manufacturing location, formulation, source and specifications of active ingredients, processing methods, manufacturing controls, container/closure system, and appearance."[8] A foreign-approved version of a U.S. biological product — no matter how similar — will almost certainly not comply with every aspect of the corresponding FDA approval and therefore as a matter of law cannot serve as the reference product in the biosimilar's comparative studies.

Some biosimilar sponsors may wish to pursue global development strategies, and FDA may want to adopt policies in the final guidance that appropriately accommodate the use of data from global development studies without contravening the BPCIA or jeopardizing patient safety. PhRMA takes the view that, in limited circumstances, data comparing a proposed biosimilar with a foreign innovator product could help corroborate a showing of biosimilarity. Accordingly, PhRMA believes that the final guidance should recommend that these data be ethically and reliably collected consistent with good clinical practice standards according to FDA and the International Conference on Harmonisation. As a matter of patient safety and sound science, the final guidance should further recommend that the foreign innovator product have the same drug substance, dose, dosage form, and route of administration as the U.S. reference

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biological medicinal products. Currently, it seems unlikely that these products may be thoroughly characterised at a molecular level. Consequently, vaccines have to be considered on a case-by-case basis.").

[5] WHO, Expert Committee on Biological Standardization, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) 4 (2009) ("This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope of this document.").

[6] PHSA § 351(i)(4) (emphasis added).

[7] The exclusivity provision of the statute also clearly indicates that the reference product must be a product licensed in the United States. For example, FDA may not approve a biosimilar application until 12 years after the date on which the reference product was first licensed under subsection (a). PHSA § 351(k)(7).

[8] *See, e.g.,* Letter from David J. Horowitz, Esq., Director, Office of Compliance, Center for Drug Evaluation and Research (CDER), FDA, to C. Bradley Stevens, President/CEO, CanadianDiscountDrugs (June 30, 2003).

product, and that it be produced by the same company that manufactures the U.S. reference product, in the same plant, using the same cell line. Although a bridging exercise (three-arm study comparing the proposed biosimilar, statutory reference product, and foreign product) might close some of the gaps, PhRMA believes that given the strong likelihood of product drifts and FDA's lack of access to the foreign product application, use of a foreign product that was not identical as just described would present an unwarranted risk to patients.

PhRMA requests that the final guidance make clear that any data from trials with a foreign product should be used only to corroborate the pivotal data comparing the proposed biosimilar to the statutorily required FDA-approved reference product. Data from trials with a foreign product should never be the sole basis of approval of the biosimilar because any other approach would effectively create two reference products: the U.S. reference product that is named in the biosimilar application and the foreign product against which the proposed biosimilar was actually evaluated. This result would violate the plain language of the BPCIA and jeopardize patient safety. The biosimilar application should therefore be approvable on the basis of comparisons to the U.S. reference product without any additional data from comparisons to a foreign product.

G. Lot Selection

The draft guidance provides that biosimilar applicants should characterize and analyze "multiple representative" lots of the proposed biosimilar product and the reference product.[9] PhRMA supports this recommendation, and we concur with the agency that the product lots should be representative of both the material used in clinical trials and in the to-be-marketed product. Nevertheless, PhRMA urges FDA to provide additional clarity regarding how the agency intends to interpret "multiple representative" lots. PhRMA recommends that, while the number of lots selected may appropriately differ on a case-by-case basis, FDA should apply the same requirements as it does to innovator biologics and, at a minimum, the number of lots should provide sufficient statistical power to detect meaningful differences in the selected quality attributes and analysis endpoints. PhRMA therefore encourages FDA to make explicit in the final guidance that statistical considerations are relevant to, and should be considered during, a determination of what constitutes "multiple representative" lots.

The draft guidance does not address the appropriate number of lots for inclusion in clinical trials. Although it is acceptable to evaluate a single lot of the reference product and may be acceptable to evaluate a single lot of the proposed biosimilar product in clinical trials, PhRMA believes it is imperative that an applicant has demonstrated batch-to-batch consistency prior to initiating clinical testing and uses the to-be-marketed product material in its clinical trials if a single lot of the proposed biosimilar is used.

H. Product Characteristics

Section 351(k)(2) of the PHSA requires that a biosimilar have the same route of administration, dosage form, and strength as its reference product. It further states that a

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[9] *Scientific Considerations* Draft Guidance, *supra* note 2, at 9.

biosimilar may be licensed only for conditions of use for which the reference product has previously been approved. The *Questions and Answers* draft guidance (A.I.4, page 5) acknowledges and discusses each of these requirements, and the *Scientific Considerations* draft guidance (Section VII.A. *Structural Analysis,* lines 352-356) specifically mentions differences in formulation between the proposed biosimilar product and reference product.

PhRMA believes that the agency's decisions regarding permissible differences in product characteristics should preserve statutory intent: that in order to justify approval under an abbreviated licensure pathway, a proposed biosimilar product must be highly similar to a single reference product, for which quality, safety, and efficacy were established on the basis of full premarket testing. Intentionally introducing changes, either during biosimilar development or to the presentation of the finished product, presents additional hurdles in the showing of biosimilarity, potentially increasing the risk of clinically meaningful differences that evade premarket detection and could place patients at risk. On the basis of both statutory and scientific considerations, PhRMA believes that the final guidance should recommend that biosimilar applicants refrain, whenever possible, from deliberately modifying controllable product design elements.

I. Analytical Testing & Structural Characterization

The draft guidance instructs an applicant to begin the biosimilarity assessment by conducting extensive structural characterization of the proposed biosimilar product and the reference product with state-of-the-art analytical techniques, and it advises that developing orthogonal, quantitative methods to detect differences will be critical. PhRMA strongly supports the agency's approach to analytical testing, and because even minor structural differences between two products can significantly affect safety, purity, and/or potency, we concur with the draft guidance that quality attributes should be evaluated through multiple analytical procedures. It is imperative that the methods employed be sensitive enough to detect differences between the proposed biosimilar product and the reference product, and PhRMA therefore encourages FDA to recommend in the final guidance that applicants use the most sophisticated and sensitive analytical methods available.

Notwithstanding the draft guidance's comprehensive recommendations, however, PhRMA believes it is important to recognize that even state-of-the-art analytical technology cannot presently identify all differences between a proposed biosimilar and the reference product. The biosimilarity of the two products thus cannot be established on the basis of analytical findings alone. Moreover, understanding the limitations of the analytical program will be critical to identifying where residual uncertainties remain and, in turn, to designing appropriate preclinical and clinical testing to resolve these questions. For this reason, PhRMA believes that the final guidance should recommend that analytical characterization be followed by preclinical and clinical testing to establish that neither identified *nor* undetected quality differences are clinically meaningful.

PhRMA also requests that the agency provide clarity in the final guidance regarding its reference to a "*fingerprint*-like analysis algorithm."[10] The reliability of analytical findings are inherently limited by the sensitivity and specificity of the methods employed. Fingerprint-like analyses, which are highly dependent on the sensitivity of the underlying analytical methods, are no different. Aggregating a collection of metrics to create a "fingerprint" provides no greater analytical information than does assessing each metric individually. For this reason, PhRMA believes that discussion of a "*fingerprint*-like" algorithm oversimplifies the stepwise process of demonstrating biosimilarity, and its inclusion risks confusing more than clarifying the necessary scope of analytical testing. We accordingly recommend that FDA remove this term from the final guidance. To the extent that discussion of a fingerprint-like analysis algorithm remains in the guidance, however, we encourage FDA to clarify its conception of this term and to make explicit that this analysis is merely one of multiple elements of a satisfactory analytical program.

J. Primary Structure

The draft guidance (Section VII.A. *Structural Analysis,* lines 322-323) states that a proposed biosimilar product should have the same amino acid sequence as its reference product, and PhRMA agrees that the amino acid sequences of the two molecules — which are controllable characteristics — should be identical. Yet, the draft guidance suggests that FDA may accept minor modifications if the applicant can demonstrate that they would not affect the product's safety and/or effectiveness. The standard for approval, however, is biosimilarity — not safety and effectiveness. Furthermore, even seemingly minor modifications may exert unintended clinical effects. Intentionally introducing changes, either during biosimilar development or to the presentation of the finished product, increases the risk of clinically meaningful differences that evade premarket detection. Accordingly, PhRMA believes that, where a biosimilar applicant introduces intentional modifications to the primary amino acid sequence, the final guidance should recommend additional comparative preclinical and clinical data to satisfy the statutory approval standard: demonstrating that the products are highly similar and not meaningfully different from a clinical perspective.

Regarding N- or C-terminal truncations specifically, PhRMA suggests that FDA clarify in the final guidance that differences in truncated forms may result from the same amino acid sequence due to clonal variations in the host cell and that the presence of truncated forms should be evaluated for any potential effects on the biosimilarity of the finished product (i.e., in particular, meaningful differences between the products in safety or effectiveness). Moreover, PhRMA believes that on a batch-to-batch basis demonstrating consistency of the proposed biosimilar is essential — that is, any variations should fall within pre-defined specifications that have been chosen to ensure that variations will not result in clinically meaningful differences. Intentional truncations of the amino acid sequence (at the level of the expression construct) complicate the demonstration of biosimilarity, and PhRMA encourages FDA to recommend in the final guidance that biosimilar applicants demonstrate that these intentional truncations are not clinically meaningful.

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[10] *Id.* at 7.

K. Higher Order Structure & Post-Translational Modifications

As the draft guidance recognizes, biologics often exhibit highly complex three-dimensional conformations, and higher order structure plays a critical role in protein function. The draft guidance thus directs biosimilar applicants to consider and address the higher order structure and post-translational modifications of the proposed biosimilar product and its reference product. Applicants are encouraged to evaluate any differences in higher order structure in terms of potential effect on protein function, particularly through functional assays.

PhRMA agrees with FDA that assessing higher order structure of a proposed biosimilar product and of the reference product is integral to a biosimilarity assessment. We also share FDA's view that certain minor differences in N- or C-terminal post-translational modifications should not preclude outright a finding of biosimilarity. We believe, however, that the biosimilar should otherwise have higher order structures that are as similar as possible to those of the reference product. Both public health and statutory considerations counsel that products approved under a 351(k) application — and therefore on the basis of abbreviated testing — should be as similar as possible in controllable elements to their reference products in order to justify relying on findings of safety and effectiveness made with respect to those reference products. Accordingly, because higher order structure is often difficult to define precisely with current analytical technology, we believe that the final guidance should recommend that biosimilar applicants assess higher order structure as thoroughly as is permitted and feasible under current science and that they minimize controllable differences in molecular identity to the maximum extent possible.

For this reason, PhRMA also encourages FDA to recommend that a biosimilar applicant demonstrate that structural features known to be essential for function be preserved in the proposed biosimilar. If they have not been preserved, additional comparative studies should be conducted. These studies should include functional assays, as the draft guidance recommends. Given the potential effect of post-translational modifications on safety and efficacy and the limitations of functional assays, however, the final guidance should recommend that in most cases, biosimilar applicants conduct clinical trials to establish that these structural differences do not significantly influence the molecule's function or have any effect on stability, dosing, immunogenicity, or clinical outcomes.

L. "Clinically Meaningful" Differences

Sections 351(k)(3) and 351(i)(2) of the PHSA require that there be no clinically meaningful differences in safety, purity, and potency between a biosimilar and its reference product. The draft guidance explains that "clinically meaningful differences" could include a difference in the expected range of safety, purity, and potency of the proposed and reference products, but that slight differences in the rates of occurrence of adverse events between the two products ordinarily would not qualify as a clinically meaningful difference. The draft guidance does not otherwise address this issue.

Because establishing the absence of clinically meaningful differences is fundamental to the statutory scheme, PhRMA urges FDA to provide additional clarity about how the agency intends to interpret and apply this requirement. In particular, because adverse events

vary by type and clinical significance, it will be important to understand whether FDA intends to compare the adverse event rate as a whole or rather by individual adverse event type. At a minimum, PhRMA believes that the final guidance should recommend that applicants conduct at least one comparative, equivalence design clinical trial involving the proposed biosimilar product and the reference product to assess whether clinically meaningful differences between the products exist.

M. Manufacturing Changes Post-Characterization

The draft guidance (Section VII.A. *Structural Analysis,* lines 345-350) states that proposed biosimilar product lots used in analytical testing should "support" the biosimilarity of material used in clinical testing, but it does not otherwise discuss the extent to which applicants may implement manufacturing process changes post-characterization.[11] PhRMA urges FDA to address this issue explicitly in the final guidance. The agency has indicated that the extent and scope of a clinical program will be based in part on the findings of the comparative analytical studies. Manufacturing changes subsequent to the analytical studies could render the analytical findings obsolete or the abbreviated preclinical and clinical program inappropriate to satisfy the biosimilar approval standard. In particular, manufacturing changes could create new or different areas of residual uncertainty regarding the structural similarity of the proposed biosimilar product and the reference product. The design of an applicant's preclinical and clinical studies might therefore cease to be appropriate to address these new areas of uncertainty. For these reasons, PhRMA urges caution with respect to any manufacturing changes post-characterization, and we believe that any manufacturing changes should require appropriate scientific justification. Accordingly, PhRMA believes that the final guidance should recommend that pre-approval process modifications subsequent to a successful CMC/quality comparison to the reference product be both minimal and minor and should note that these modifications may necessitate additional analytical comparisons of the proposed biosimilar to the reference product.

Moreover, the reference product may also undergo manufacturing changes during the period of biosimilar development that would be unknown to the sponsor of the proposed biosimilar product. These changes, too, could affect the biosimilarity demonstration. For this reason, the final guidance should make clear that biosimilarity assessments should be relevant to the currently marketed reference product at the time of submission of a marketing application.

PhRMA concurs with the draft guidance's recommendation that an applicant bridge the lots used in analytical testing with the material evaluated in clinical trials and with the proposed commercial product. This provides an additional measure of assurance that reliance on an analytical finding to tailor subsequent clinical testing is scientifically justified. We note, however, a discrepancy between the applicant's obligations described in the *Scientific Considerations* draft guidance and the applicant's obligations described in the *Quality Considerations* draft guidance: the former discusses bridging to clinical material used in all

[11] *Id.* at 9.

"confirmatory clinical trials," whereas the latter limits it to "the principal clinical trial."[12] PhRMA supports the statement in the *Scientific Considerations* draft guidance, and we have commented separately in the *Quality Considerations* guidance docket to recommend incorporation of this language into the *Quality Considerations* final guidance.

N. Functional Assays

The draft guidance recommends that the biosimilar applicant conduct extensive comparative functional evaluations of the proposed biosimilar product and the reference product, which PhRMA supports. *In vitro* functional testing is an integral component of the biosimilarity assessment that can provide information about the biological activities and potency of the proposed biosimilar product and that may reveal critical differences in function or mechanism of action compared to the reference product. PhRMA further agrees with FDA that the employed assays should be sensitive to changes in functional activities of the proposed biosimilar product and that the import of the functional findings will be affected by the assays' sensitivity, specificity, and extent of validation.

PhRMA questions, however, the scientific basis for the statement in the draft guidance that "[s]ponsors can use functional assays . . . to demonstrate that there are no clinically meaningful differences between the proposed biosimilar product and the reference product."[13] In particular, PhRMA would not be supportive of any suggestion that functional testing may obviate entirely the need for a clinical program. Functional assays are a valuable tool for evaluating biological activity but, as the draft guidance itself recognizes, may fail to fully capture the clinical activity of a protein. For this reason, the final guidance should recommend that applicants conduct at least one comparative, equivalence design clinical study involving the proposed biosimilar product and the reference product in order to establish that a proposed biosimilar does not possess clinically meaningful differences in safety, purity, and potency from the reference product, as is legally required for approval.

O. Preclinical Animal Testing

The draft guidance (Section VII.C. *Animal Data*, lines 395-397) instructs that, unless waived, a biosimilarity assessment should include preclinical data derived from animal studies. This testing may include toxicity studies, animal PK and PD measures, and immunogenicity studies.

PhRMA believes that preclinical testing is integral to identifying product differences that warrant evaluation in subsequent clinical trials, and we support the types of animal studies outlined by the draft guidance. PhRMA is concerned, however, by the draft guidance's suggestion that preclinical animal testing might be waived in some circumstances. PhRMA recognizes the limitations of animal testing in some particular circumstances, most

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[12] *Id*; FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," *Draft* (Feb. 2012), at 13 (hereafter the "*Quality Considerations* Draft Guidance").

[13] *Id.* at 10.

notably where a pharmacologically relevant species is unavailable for scientific reasons. Nevertheless, PhRMA believes that animal testing remains an essential step in demonstrating biosimilarity. Patient safety considerations counsel that the first testing of a biological product (innovative or biosimilar) should not occur in human subjects. Animal toxicity or safety testing may detect differences between products that were not detected through analytical testing, including differences with respect to inactive ingredients, contaminants, and the presence of aggregates. In PhRMA's view, the lack of a relevant species should not trigger a waiver of preclinical animal studies, but should instead trigger a scientific discussion, on a case-by-case basis, about the appropriate size of and most appropriate species for the necessary preclinical animal studies. Accordingly, PhRMA suggests that the final guidance recommend that:

1. The biosimilar applicant generally perform an *in vivo* evaluation of toxicity or safety in a non-human species. In light of human subject safety considerations, such an evaluation may remain appropriate even when there is no relevant target. The size of the study and study duration should be scientifically justified and of sufficient size and length to detect differential toxicity, consistent with the principles stated in ICH S6 guidance and addendum ICH S6(R1). Consistent with recommendations in ICH S6(R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) for monoclonal antibodies and other related antibody products directed at foreign targets (i.e., bacterial, viral targets, etc.), PhRMA believes that a short-term safety study in a single species or in an animal model of disease should be considered prior to human dosing with a biosimilar and, where this is not feasible, appropriate risk mitigation strategies should be adopted for clinical trials.

2. The biosimilar applicant consider conducting animal PK and PD assessments, which — as the draft guidance explains — may be helpful to demonstrating biosimilarity. PhRMA strongly agrees with the agency, however, that this testing will not negate the need for human PK and PD studies.

3. Comparative animal toxicology studies include an immunogenicity assessment to aid in interpretation of the toxicology and PK data. Although, as the agency notes, animal immunogenicity assessments may not predict immunogenic responses to protein products in humans, PhRMA supports the draft guidance's conclusion that this information may nevertheless be useful and relevant to patient safety. It may also be reasonable to incorporate pharmacodynamic endpoints into the toxicology studies to help interpret the toxicology and PK data.

Further, given the reasonable expectation of study subjects that a pharmaceutical has been robustly tested in non-human animals prior to study initiation, PhRMA believes that the final guidance should recommend that study enrollees be fully informed via the informed consent process if a biosimilar has not undergone preclinical animal testing.

P. Clinical Testing

FDA may not approve a proposed biosimilar if there are clinically meaningful differences in safety, purity, or potency between that product and its reference product. Because a biosimilar will be similar, but not identical, to the reference product, however, the two products

cannot be assumed to have the same clinical profile. And given the current state of the science, clinical testing remains the most robust and reliable method for detecting clinical differences that would preclude approval under section 351(k). For these reasons, and because the default rule under the statute is that each biosimilar application requires data from clinical testing, PhRMA supports the draft guidance's recognition that biosimilar applicants bear the burden of demonstrating why clinical trial waivers are scientifically justified. We remain highly concerned, however, by the frequent references in the draft guidance to circumstances in which FDA may waive clinical testing requirements. As discussed more fully below, PhRMA remains of the firm belief that both statutory and patient safety considerations necessitate at least one comparative, equivalence design clinical trial, as well as clinical immunogenicity testing, for biosimilar approval. Moreover, in the absence of strong scientific justification, clinical data should be necessary to support each indication for which the biosimilar seeks approval.

The draft guidance instructs that comparative PK and PD studies are "fundamental" to the biosimilarity assessment and will generally be expected, a position that PhRMA supports.[14] The final guidance should recommend that biosimilar applicants carefully consider the study endpoints in conjunction with the selection of margins for a finding of "biosimilarity" and clearly justify and pre-define the margins, likely on a product-by-product basis. Moreover, PhRMA believes that any candidate PD measure(s) must be sensitive enough to detect *in vivo* differences between the proposed biosimilar product and the reference product, and we support the draft guidance's recommendation that PD measures should be clinically relevant and validated as a surrogate for efficacy.

Notwithstanding the importance of foundational PK (and PD) studies, the complex structures of biologics and the mechanisms by which they penetrate tissues mean that a demonstration of PK similarity, in and of itself, is not sufficient to establish the absence of clinically meaningful differences. For this reason, PhRMA does not support the draft guidance's statement that human PK and PD studies may alone provide sufficient clinical data to support a finding of "biosimilarity" as that term is defined in the statute. Rather, we believe that the final guidance should state that, in order to establish that there are no clinically meaningful differences between the products, as is legally required, a biosimilar applicant should provide the results from at least one comparative clinical trial with the reference product of adequate size and with appropriate endpoints to detect small differences in safety and efficacy. (As discussed in the next section, comparative clinical data should also be provided for each approved indication of the U.S. reference product for which the biosimilar applicant seeks approval, except where extrapolation is scientifically justified.)

PhRMA concurs with FDA that this study should generally employ an equivalence design, which permits a more robust efficacy comparison. We encourage FDA to specify in the final guidance that efficacy margins should be pre-specified and selected based on the largest difference in efficacy that is considered to have no clinical relevance — i.e., that would not matter in clinical practice. The use of both upper and lower margins, as the draft guidance acknowledges, will reveal both decreased and increased efficacy of the proposed

[14] *Id.* at 13.

biosimilar relative to the reference product. In PhRMA's view, a biological product that is shown to have a level of efficacy outside the upper equivalence margin would be inappropriate for approval under the 351(k) pathway. We believe it is imperative that biosimilar applicants use clinical efficacy endpoints that are the most sensitive to detecting differences (which may not necessarily be the same as those used in the reference product's trials), and we encourage FDA to make this recommendation explicit in the final guidance. PhRMA also agrees with the draft guidance that in some cases different endpoints, including surrogate and pharmacodynamic markers, may be appropriate. Where pharmacodynamic or surrogate endpoints are employed, however, the final guidance should recommend that they be supported by adequate clinical data to demonstrate that they correlate with clinical outcomes.

Finally, understanding immunogenicity differences between a proposed biosimilar product and the reference product will be essential to patient safety. Thus, while PhRMA supports the draft guidance's instruction that at least one comparative, clinical immunogenicity assessment will "generally" be expected, we cannot envision a scenario in which FDA could appropriately conclude that a proposed biosimilar is as safe as the reference product without clinical immunogenicity testing.[15] PhRMA believes that the final guidance should recommend that this immunogenicity program generally include both premarket and some postmarket testing. For chronically administered agents, the length of the premarket immunogenicity assessment should be carefully evaluated, given that antibodies may develop over several months and that the adequacy of the premarket immunogenicity assessment is dependent on the ability to evaluate potential immunogenicity issues associated with chronic use. Testing should evaluate both binding and neutralizing antibodies, as the draft guidance recommends. It should also compare cross-reactivity and target epitopes of immune responses, as well as the severity of clinical consequences. These and other features may cause two products' safety or effectiveness profiles to differ, even if the rate of immunogenicity associated with the products is the same. Moreover, FDA should recommend in the final guidance that immunogenicity be assessed using the proposed biosimilar agent as reagent; otherwise antibodies to the proposed biosimilar may go undetected.

In addition, PhRMA urges caution regarding one-sided trial designs, which the draft guidance (Section VII.D.4. *Clinical Study Design Issues,* lines 564-567) indicates will generally be acceptable. Although it is true that one-sided trial designs will detect biosimilars with greater immunogenic potential relative to the reference product, they will fail to identify biosimilars that are less immunogenic. A less immunogenic biosimilar could exhibit heightened efficacy compared to the reference product, and it could increase a patient's exposure to active drug (due either to fewer binding and neutralizing antibodies or reduced drug clearance). In both circumstances, patients treated with the biosimilar might be exposed to functional dosages at the upper therapeutic range, thereby increasing the potential rate and severity of non-immunological adverse events. A finding that a proposed biosimilar is less immunogenic than its reference product, too, may signal that other, undetected differences exist between the products. PhRMA therefore encourages FDA to recommend, in the final guidance, that a biosimilar applicant generally assess immunogenicity in a two-sided trial. The guidance should also recommend that

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[15] *Id.* at 14.

if a proposed biosimilar is less immunogenic than the reference product, the applicant demonstrate that this is not associated with clinically meaningful differences. Further, the final guidance should recommend that if a one-sided design is nevertheless used, the acceptable error for increased immunogenicity be the same as it would have been had an equivalence design been used.

Moreover, where extrapolation of efficacy to another approved indication of the reference product is sufficiently scientifically justified, the final guidance should recommend that applicants investigate immunogenicity in the patient population that is most sensitive to immune responses. This study should evaluate the nature of the immunogenicity (e.g., cross-reactivity, target epitopes, and neutralizing activity), as discussed above. Because even robust premarket immunogenicity trials will not be able to detect all immunogenic reactions, particularly rare immune-related adverse events, the final guidance should state that timely postmarket surveillance will also generally be expected..

Q. Extrapolation of Clinical Data Across Indications

Where a biosimilar meets the requirements for licensure for one condition of use, the draft guidance encourages sponsors to be "cautious" with respect to extrapolation of clinical data to support a different condition of use.[16] Extrapolation would, however, be permitted where a sponsor provides "sufficient scientific justification."[17] The draft guidance explains that any justification should address the mechanism of action in each condition of use; the PK and bio-distribution of the product in different populations; differences in expected toxicities in each condition of use and patient population; and any other factor that may affect safety or effectiveness of the product in each condition of use and population for which approval is sought.

PhRMA supports the position in the draft guidance (Section VII.D.5. *Extrapolation of Clinical Data Across Indications,* lines 760-767) that extrapolation will require scientific justification, and we believe that appropriate clinical data will generally be necessary for every indication of the biosimilar. This scientific justification should be sufficiently rigorous and thorough to provide adequate certainty that safety and efficacy data from a studied indication can predict the safety and efficacy of a proposed biosimilar in an unstudied indication. PhRMA believes that the final guidance should recommend that applicants study the patient population(s) most sensitive to differences in safety, efficacy, and immune response, as these patient populations may be different and the study of multiple sensitive patient populations may be necessary to justify extrapolation. The final guidance should further recommend that applicants provide scientific justification as to why the indication(s) and patient population(s) studied clinically are the most sensitive indication(s) and patient population(s) of the indications for which licensure is sought. The biosimilar applicant should also include a demonstration that there are no significant differences between the PK and bio-distribution of the product in all indications and patient populations for which it seeks licensure. In addition, as a scientific

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[16] *Id.* at 20.

[17] *Id.* at 19.

matter, PhRMA believes that extrapolation across indications that do not share the same molecular mechanism of action or where the mechanism of action is not well understood cannot be justified. Restricting extrapolation to indications that share the same, well-defined mechanism of action will help to ensure that the two disease states are similar and well understood. This will, in turn, increase the likelihood that clinical similarity in the studied indication supports clinical similarity in the un-studied indication. We accordingly request that the final guidance elevate mechanism of action from one of multiple considerations to a prerequisite for extrapolation.

Moreover, extrapolation of data from one population *within an indication* to another population *within that same (or to a closely related) indication* is different from extrapolation of data *across truly different indications*. We urge caution in permitting extrapolation with respect to either efficacy or safety (particularly immunogenicity) in the latter case — because of potential differences in pathophysiology and in (tissue) site of action, as well as potential differences in comorbidities and concurrent therapies in the patient populations. PhRMA encourages FDA to specify additional factors relevant to the determination whether extrapolation across indications in these cases is scientifically justified. We recommend that FDA indicate in the final guidance that the quality and amount of data that the applicant has provided to support the first indication will be a principal consideration. Other factors should include whether the mechanisms of disease are the same, whether the indications share the same disease state (e.g., immunocompetent, immunosuppressed, etc.), whether the indications have similar risk/benefit ratios, whether the indications share the same route of administration, whether the patient populations differ in age or other factors that may make one population more sensitive to differences between products than the other, whether the indications involve different doses or dosing regimens, whether the indications involve penetration into different tissues, and the extent of comparative characterizations of the molecules using current analytical methods. In addition, we believe, and encourage FDA to note in the final guidance that extrapolation from an indication that has a high risk/benefit ratio to an indication that has a low risk/benefit ratio would likely be more scientifically justified than extrapolation from an indication with a low risk/benefit ratio to an indication with a high risk/benefit ratio.

R. Labeling

Product labeling is the primary vehicle for communicating information about medicinal products to healthcare professionals, and we therefore agree with the draft guidance that biosimilar labeling should include all information "necessary for a health professional to make prescribing decisions."[18] PhRMA supports the draft guidance's recommendation that biosimilar product labeling include a clear statement that the product is a biosimilar to a reference product for a stated indication and route of administration and indicate whether the product has been deemed interchangeable with the reference product. As stated in our 2010 comments to the Part 15 hearing docket, however, we continue to believe that additional labeling information is necessary for health professionals to make informed prescribing decisions. Specifically, PhRMA believes that the final guidance should recommend that product labeling

[18] *Id.* at 21.

disclose which of the biosimilar's indications were supported by clinical data and which were based on extrapolation, as well as how much (and what type of) clinical data supported the product's approval. And due to the risk of unsafe and inappropriate substitution of a non-interchangeable biosimilar with the reference product, the labeling should state prominently that a non-interchangeable biosimilar should not be substituted for the prescribed product without the express consent of the treating physician.

As implementation of the BPCIA continues, stakeholders will need clarity regarding the information that must be included in biosimilar package inserts. We encourage FDA to address these issues soon and support the development of guidance on biosimilar package inserts.[19] We look forward to participating when draft guidance is released.

S. Pharmacovigilance and Other Postmarket Safety Considerations

PhRMA supports the draft guidance's recognition that robust postmarket safety monitoring will be integral to ensuring the safety of biosimilar products (Section VIII. *Postmarketing Safety Monitoring Considerations*). The pharmacovigilance plan for each approved biosimilar should be tailored to the risk and benefit profile of that product (which should, as a statutory matter, be the same as the risk/benefit profile of the reference product). PhRMA also endorses the factors that FDA has indicated should guide pharmacovigilance plan development. We encourage FDA also to identify in the final guidance the extent to which immunogenicity concerns have (or have not) been addressed in premarket testing as a primary consideration in FDA's evaluation of proposed pharmacovigilance approaches.

As the draft guidance helpfully recognizes, a pharmacovigilance plan should have "adequate mechanisms in place to differentiate between the adverse events associated with the [biosimilar] product and those associated with the reference product."[20] PhRMA believes that distinct nonproprietary names for biosimilars are critical to ensuring this differentiation, a point that we address more fully in Section III. We appreciate FDA's recent indication that it will address naming in future guidance, and we urge the agency at that time to recommend unique names for biosimilars. National drug codes (NDCs) and lot numbers are helpful, but cannot ensure the same level of pharmacovigilance, because patients and healthcare professionals will not as readily have access to this information and because both prescribing and adverse event reporting are primarily conducted by established or brand name and not by NDC.

PhRMA also supports FDA's recognition that postmarket studies and risk evaluation and mitigation strategy (REMS) programs may at times be required as part of broader postmarket safety monitoring. In particular, we agree that rare safety risks, in particular immunogenicity, may warrant evaluation through postmarket studies. And we believe that the final guidance should recommend that where a reference product is subject to a REMS, the

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[19] *See,* FDA "Biosimilars Guidance Meeting Webinar," Video Recording (Feb. 15, 2012), at min. 33:00, *available at:* https://collaboration.fda.gov/p13473376/?launcher=false&fcsContent=true&pbMode=normal (stating that FDA intends to issue guidance on package inserts at a future date).

[20] *Scientific Considerations* Draft Guidance, *supra* note 2, at 20.

biosimilar product generally have a REMS that is at least as rigorous. Further, although a biosimilar cannot lawfully be approved if there are clinically meaningful differences between it and its reference product, undetected differences may emerge in the postmarket period — for example, due to the abbreviated premarket program for the biosimilar, due to extrapolation, or due to product drift. In some cases, therefore, public health considerations may necessitate a REMS that is more extensive than the REMS of the innovator product. We believe this possibility — and the agency's authority to shape postmarket commitments as necessary to ensure the safety of patients — should be expressly acknowledged.

III. Additional Comments

PhRMA offers comments on four issues not raised directly in the draft guidance: (1) naming of biosimilars; (2) inappropriate substitution of biosimilars not deemed interchangeable with the reference product; (3) the inherent differences between biosimilar applications and BLAs; and (4) the agency's limited but nonetheless pivotal role with respect to section 351(l) of the PHSA. PhRMA raised each of these issues in its December 2010 comments and continues to believe that addressing them is integral to successful implementation of the BPCIA. PhRMA believes that FDA should address these issues in the final guidance documents, in updates to the *Questions & Answers* guidance, or in future draft guidances.

First, we appreciate FDA's recent indication that it will address naming in guidance later this year, and we urge the agency at that time to require unique names for biosimilars. As discussed previously, the draft guidance recognizes that a pharmacovigilance plan should have "adequate mechanisms in place to differentiate between the adverse events associated with the [biosimilar] product and those associated with the reference product."[21] Distinct nonproprietary names for biosimilars are critical to ensuring this differentiation. National drug codes (NDCs) and lot numbers are helpful, but cannot ensure accurate pharmacovigilance because patients and healthcare professionals will not as readily have access to this information and because both prescribing and adverse event reporting are done by drug or product name and not by NDC. Unique names will also help prevent errors in the distribution, prescribing, dispensing, and administration of biologics, as well as to prevent inadvertent substitution of non-interchangeable products. They may also be helpful in efforts to ensure that physician selection of treatment is respected. And they will help facilitate recalls and appropriate reimbursement policies.[22]

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[21] *Id.*

[22] The EMA action on erythropoiesis stimulating agents (ESAs) demonstrates the importance of unique names for biosimilars. After two cases of pure red cell aplasia (PRCA) occurred during a clinical study investigating ESAs, the EMA imposed labeling changes for the three epoetin alfa ESA biosimilars in August 2010. The Summary of Product Characteristics was amended to include a statement warning healthcare professionals of the importance of traceability: "In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file." *See* EMA, Binocrit, Procedural steps taken and scientific information after the authorisation (Updated Aug. 18, 2010). The patient Package Leaflet was amended to warn patients to "[t]ake special care with (continued...)

For these reasons, PhRMA continues to believe that FDA should ensure that each biosimilar's labeling and packaging bears a nonproprietary name that differentiates it from the reference product and other biosimilars. It remains unclear whether biosimilars will consistently receive distinct International Non-Proprietary Names (INNs) from the WHO or distinct United States Adopted Names (USANs) from the USAN Council. FDA should therefore assume that, unless it takes steps to address naming, some biosimilars will have nonproprietary names that are the same as the nonproprietary names of their reference products and other biosimilars, while others will have names that are different.

PhRMA supports the use of common stems for nonproprietary names of related products and either suffixes or prefixes to distinguish between the reference product and a biosimilar and among multiple biosimilars. This approach appropriately strikes the balance between indicating that these products are related, on the one hand, and confirming that they are not the same, on the other hand.

Second, FDA should take steps to prevent the inappropriate substitution of biosimilars that have not been found interchangeable to their reference products. Substitution of non-interchangeable products could cause potentially serious clinical problems, particularly where substitution occurs without the knowledge of the treating physicians. PhRMA believes that, as with preserving effective pharmacovigilance, unique nonproprietary names for the reference product and biosimilar product will be critical to preventing inappropriate substitution of non-interchangeable products. 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 under applicable state law. The final guidance should recommend that this policy statement appear clearly in the labeling for biosimilars, on the agency's website, and in letters to healthcare professionals, pharmacies, formularies, and states.

Third, PhRMA continues to urge the agency to take steps to articulate explicitly and maintain the clear distinction between applications filed under section 351(a) (BLAs) and applications filed under section 351(k) (biosimilar applications) of the PHSA. As amended, section 351 now describes two mutually exclusive and fundamentally different pathways to market. The core concept of section 351(k) is that a product that is highly similar to a previously approved product, and that has the same mechanism of action, route of administration, dosage form, strength, and conditions of use as the previously approved product, may be approved in part based on FDA's finding that the previously approved product was safe, pure, and potent. This abbreviated application is, however, subject to various constraints, including the 12-year exclusivity term of the reference product sponsor and the premarket patent litigation process that may result in a statutory injunction. By way of contrast, FDA has long and consistently taken the position that applications submitted under section 351(a) may not rely on data and findings

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other products that stimulate red blood cell production: [Biosimilar name] is one of a group of products that stimulate the production of red blood cells like the human protein erythropoietin does. Your healthcare professional will always record the exact product you are using." *Id.* According to the EMA, the agency "considered it important that accurate medication histories are maintained for patients treated with epoetins, recording the trade name or the scientific name with the name of the manufacturer." *Id.*

relevant to another product — that the section requires original and comprehensive applications demonstrating product safety, purity, and potency. They are not subject to exclusivity barriers (apart from orphan exclusivity) or to premarket patent litigation.

It would upset the careful balance struck by Congress between biosimilar market entry and additional price competition, on the one hand, and incentives for biological product innovation, on the other hand, if FDA allowed section 351(a) applications to rely on prior approvals and thereby, indirectly, on the work of earlier applicants. This would give the biosimilar applicant the benefits of an abbreviated pathway without imposing the associated burdens (exclusivity and premarket patent litigation). Such an approach would also raise grave issues under the takings clause of the U.S. Constitution, and it might conflict with U.S. treaty obligations. The agency might also face liability under the Administrative Procedure Act for acting arbitrarily, if it reversed its longstanding position with respect to applications under section 351(a) or if it approved applications that were functionally biosimilar applications under two different provisions of the statute.[23]

FDA should therefore take steps to ensure that applications are properly categorized by their sponsors and the agency, no matter how they are characterized in the public domain. These steps could include — among other things — a refusal-to-file policy for ordinary BLAs that ensures the use of the biosimilar pathway for any application that relies, implicitly or explicitly, without consent, on previously submitted data or the fact of a prior approval. For example, the agency could take the position that an application is presumptively a biosimilar application if: (1) the application proposes a product that is claimed to have the same mechanism of action, route of administration, dosage form, strength, and conditions of use as a previously approved product and (2) that application contains analytical and quality data comparing the product to the previously approved product and thus relies directly or indirectly on the safety and efficacy data in, or FDA approval of, the BLA for the previous product.

Fourth, PhRMA continues to believe it essential that the agency ensure the BPCIA as a whole functions as intended — specifically, that applicants under section 351(k) comply with the obligations imposed by section 351(l). FDA guidance should therefore recommend that each applicant include with its biosimilar application a certification that it will, within 20 days after notification has been received that the application was accepted for review, in accordance with section 351(l)(2), provide the reference product sponsor with a copy of the application and information describing the processes used to manufacture the biosimilar product. FDA should also require that the applicant amend the pending application on the 20th day with a certification that it has done so, and the agency should refuse to further process any application that fails to include the second certification.

Implementing a certification requirement would not impose a substantial burden on the agency, and yet it would play a vital role in ensuring the scheme works as intended by Congress. The core concept of section 351(k) is that a biosimilar applicant may avoid performing the full preclinical and clinical testing that is required for a full section 351(a)

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[23] *See, e.g., Bracco Diagnostics, Inc. v. Shalala,* 963 F. Supp. 20, 28 (D.D.C. 1997) (finding the disparate treatment of similarly situated products to be arbitrary and capricious).

application. The BPCIA compromise, however, is that innovators receive 12 years of exclusivity and a meaningful opportunity to litigate patent infringement issues prior to biosimilar market entry. And there can be no question that biosimilar applicants must by law provide their applications and manufacturing information to reference product sponsors. The provision requiring this — section 351(l)(2) — is unambiguously mandatory.[24] Further, the balance of the scheme imposes obligations on biosimilar applicants and reference product sponsors that flow directly from the provision in question.[25] Just as it would undermine the compromise for applicants to rely on prior approvals in applications they file under section 351(a) without waiting out the exclusivity term, it would thwart the compromise for applicants to rely on prior approvals in section 351(k) applications while ignoring the statutory obligation to provide the information needed for meaningful premarket patent litigation. PhRMA believes it is incumbent on FDA to ensure the scheme works as intended by declining to process submissions of applicants who thwart the core compromise by avoiding either exclusivity or premarket patent litigation. A certification obligation would not engage FDA in patent disputes, would be simple for FDA to administer, and would be just as ministerial as the sole explicit role for the agency under section 351(l) — accepting notice and a copy of any patent infringement complaint served under the statute's "immediate patent infringement action" provisions and publishing notice of that complaint in the *Federal Register*.

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[24] *See* PHSA § 351(l)(2) ("Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant . . . *shall* provide . . .") (emphasis added).

[25] *E.g.*, PHSA § 351(l)(3) ("Not later than 60 days *after the receipt of the application and information under paragraph (2)* . . .") (emphasis added).

IV. Conclusion

PhRMA appreciates FDA's issuance of draft guidance on the scientific considerations relevant to establishing biosimilarity and the opportunity to comment. We look forward to a continued dialogue on the important issues raised by this, and the two related, biosimilar draft guidances, and we hope the agency continues to solicit public, transparent stakeholder input as it implements the BPCIA.

If you have any questions, please do not hesitate to contact us.

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