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Re: Docket No. FDA-2011-D-0602: Draft Guidance for Industry on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product; 77 Fed. Reg. 8884 (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Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to FDA's issuance of draft guidance for industry entitled "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" ("*Quality Considerations* draft guidance" or the "draft guidance").[1] PhRMA is a voluntary, nonprofit association that represents the country's leading pharmaceutical research and biotechnology companies, which are devoted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to developing, manufacturing, and approving biosimilars, we applaud FDA's decision to seek public input by issuing this draft guidance, as well as two additional draft guidances, on implementation of the BPCIA and the considerations relevant to establishing biosimilarity. We are pleased to offer the following comments on the draft guidance, and we hope that FDA will continue to seek stakeholder input openly and transparently as it implements the BPCIA.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. 8884 (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. 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.

B. Relationship Between Biosimilarity & Comparability Demonstrations

PhRMA appreciates FDA's recognition that biosimilarity demonstrations between proposed biosimilar and reference products are distinct from, and may require more extensive and comprehensive data 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.

While the *Scientific Considerations* draft guidance includes a similar discussion about the relationship between biosimilarity and comparability demonstrations, it recognizes explicitly that a biosimilarity demonstration will "typically be more complex than" a comparability demonstration.[2] Furthermore, whereas the *Quality Considerations* draft guidance recognizes that more data *may* be required for biosimilarity demonstrations, the *Scientific Considerations* draft guidance states that more data and information generally "*will* be required to establish biosimilarity."[3] PhRMA believes that the comments in the *Scientific Considerations* draft guidance are important and accurate and should be incorporated into this guidance, so that the two guidances are better aligned.

C. 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 (Section IV. *Definitions*, pages 5-6), 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

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[2] FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," *Draft* (Feb. 2012), at 5 (hereafter the "*Scientific Considerations* Draft Guidance").

[3] *Id.* at 6 (emphasis added); FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," *Draft* (Feb. 2012), at 3 (hereafter the "*Quality Considerations* Draft Guidance").

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.

D. 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 notes (Section III. *Scope*, lines 164-168) that if a *particular* reference product cannot be adequately characterized, applicants should "consult" with FDA about whether a 351(k) application is appropriate.[4] But it takes no position on particular product classes.

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 supports 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

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[4] *Quality Considerations* Draft Guidance, *supra* note 3, at 4.

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.[5] And vaccines are excluded from the scope of the WHO guidelines on biosimilar products.[6]

E. 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)."[7] 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).[8] This means that any

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[5] *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 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.").

[6] 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.").

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

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."[9] 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 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

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[8] 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).

[9] *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).

basis of comparisons to the U.S. reference product without any additional data from comparisons to a foreign product.

F. Lot Selection

The draft guidance provides that biosimilar applicants should characterize and analyze an "appropriate" number of lots of the proposed biosimilar product and the reference product.[10] 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 an "appropriate" number of 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 an "appropriate" number of 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.

G. 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 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 *Quality Considerations* draft guidance (Section VI.H. *Finished Drug Product*, lines 573-582) 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

[10] *Quality Considerations* Draft Guidance, *supra* note 3, at 7.

applicants refrain, whenever possible, from deliberately modifying controllable product design elements.

H. Reference Standards

The draft guidance encourages applicants to perform comparisons with reference standards. Specifically, it recommends that biosimilar applicants compare a proposed biosimilar product to reference standards for selected attributes during quality testing. It also states that where a "suitable, publicly available, and well-established" reference standard for the protein exists, a physicochemical and/or functional comparison to that standard should be performed.[11] Although PhRMA recognizes that comparisons to reference standards provide an additional measure of assurance that a proposed biosimilar has been robustly characterized, comparison with a reference standard will not demonstrate similarity to the reference product. As the draft guidance appropriately conveys, even where a published reference standard exists, direct comparisons with the reference product remain necessary. And as FDA has previously recognized in the context of other complex products, reference standards may fail to capture fully a product's relevant attributes and biologically active components.[12] While a reference standard comparison may thus provide an *additional* data point in the biosimilarity assessment, it may never supplant the BPCIA's requirement for *original*, direct comparisons with the U.S.-licensed reference product.

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

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[11] *Id.*

[12] For example, in 1997 FDA determined that abbreviated new drug applications (ANDAs) for synthetic conjugated estrogens were not appropriate because the active ingredients in the reference product, Premarin, could not be adequately characterized and were found to be greater in number than previously believed. The agency's position contradicted the USP monograph for conjugated estrogens, which since its inception had defined conjugated estrogens as containing only two active ingredients: sodium estrone sulfate and sodium equilin sulfate. FDA recognized that new scientific information may render monographs outdated and concluded that it could "no longer support the position taken in the current USP monograph." *See,* CDER, "Synthetic Conjugated Estrogens: Questions and Answers," May 15, 1997, *available at:* http://www.fda.gov/ohrms/dockets/dockets/98p0311/Tab0025.pdf. In the preamble to the final ANDA regulations, the agency explained that "in some cases, FDA may prescribe additional standards [beyond those contained in public reference standards] that are material to the ingredient's sameness." 57 Fed. Reg. 17950, 17959 (Apr. 28, 1992).

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 requests that the agency provide clarity in the final guidance regarding its reference to a "fingerprint-like analysis algorithm."[13] 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. Cell Type & Expression System

The draft guidance (Section VI.A. *Expression System*, liens 371-375) instructs applicants to carefully consider differences between the chosen expression system for the biosimilar and that of the reference product. It also signals that the agency may be receptive to differences in cell type.

The details of the expression construct used to produce the reference product may not be publicly known, and as FDA notes there are likely to be differences between the expression systems of the proposed biosimilar and reference product. PhRMA agrees with FDA that the principles of ICH Q5B provide sufficient guidance to biosimilar applicants in their characterization of the chosen expression construct. As the agency notes, however, the choice of expression system will significantly affect the types of process-related and product-related substances, impurities, and contaminants that result, as well as the types and extent of translational and post-translational modifications. Thus, PhRMA believes that the final guidance should recommend additional testing, likely including clinical study(ies), where a different

[13] *Quality Considerations* Draft Guidance, *supra* note 3, at 8.

expression construct is used, and it should note that resulting differences between the two products might ultimately preclude a finding of biosimilarity (i.e., might result in use of the 351(a) pathway).

The cell type used to manufacture the reference product, by way of contrast, is public knowledge, and differences in host cell type are entirely avoidable. Moreover, employing a different host cell type from that of the reference product could precipitate clinically meaningful differences between the biosimilar and its reference product that would be impossible to anticipate or detect analytically at this time. These differences — like those resulting from use of a different expression construct — could include both product-and process-related impurities and contaminants, which have the potential to increase the immunogenic profile of the biosimilar. PhRMA believes that the final guidance should note explicitly that additional analytical, preclinical, and clinical studies may be necessary to investigate potential differences introduced by a change in cell type. And in view of the purpose of the BPCIA — to authorize an abbreviated licensure pathway for biologics that are highly similar to previously licensed reference products — PhRMA encourages FDA to state more plainly in the final guidance that applicants should avoid controllable process and design differences, such as cell type, to the extent feasible.

K. Primary Structure

The draft guidance (Section VI.A. *Expression System*, lines 368-369) states that a proposed biosimilar product should have the same primary 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.

L. 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.

M. Testing of Drug Substance Versus Finished Product

The draft guidance instructs applicants to characterize the "most downstream intermediate" best suited to the analytical method employed, provided that the evaluated attribute(s) remains stable through further processing steps.[14] For these reasons, the draft guidance (Section VI.H. *Finished Drug Product*, lines 562-563) states characterization will generally be performed on bulk drug substance. Depending on the particular analysis, however,

[14] *Id.* at 14.

applicants may characterize the finished drug product, and at times it "may be called for" that applicants analyze both the "isolated drug substance and the finished drug product."[15]

PhRMA generally endorses the approach described by FDA, although we suggest that the final guidance recommend that applicants analyze the finished drug product whenever possible. As the agency recognizes, proteins are extraordinarily sensitive to their environment and processing conditions. It may not always be possible to establish prospectively that attributes will remain stable through subsequent processing steps, particularly where there is exposure to new materials in the container closure system and/or finished dosage form. Analytical characterization of the finished dosage form of the proposed biosimilar product and the reference product would help to alleviate these concerns.

PhRMA acknowledges, however, that finished drug product may be unsuited to certain analyses. In these instances, we recommend that FDA refer to characterization of the "extracted protein" — rather than the "drug substance" — of the proposed biosimilar product and the reference product. For most biosimilar development programs, true drug substance from the reference product will not be available for analysis. Requiring the reverse engineering of reference product drug substance may result in a sample from which data would be difficult to interpret and could be unreliable. Moreover, as the draft guidance notes, the analysis of drug substance presents an additional scientific challenge because extraction and isolation for analytical testing may alter key molecular attributes of the product. PhRMA strongly supports the draft guidance's recommendation, however, that applicants fully describe the extraction process when an extracted protein is used in place of the finished drug product. And we encourage FDA to state in the final guidance that applicants should provide robust support that the process does not alter product quality.

N. Manufacturing Changes Post-Characterization

The draft guidance 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.[16] 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

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[15] *Id.*

[16] *Id.* at 13.

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 "confirmatory clinical trials," whereas the latter limits it to "the principal clinical trial."[17] PhRMA urges FDA to affirm the statement in the *Scientific Considerations* draft guidance by clarifying in the *Quality Considerations* final guidance that the bridging recommendation applies to proposed biosimilar product tested in any clinical trial.

O. Functional Assays

The draft guidance (Section VI.D. *Functional Activities*) 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.

Although the issue is not discussed explicitly in the *Quality Considerations* draft guidance, the *Scientific Considerations* draft guidance states 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."[18] PhRMA would not support 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

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[17] *Id.*

[18] *Scientific Considerations* Draft Guidance, *supra* note 2, at 10.

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.

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. The *Scientific Considerations* 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."[19] 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.[20]

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[19] *Id.* at 20.

[20] 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 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 (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 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.

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are maintained for patients treated with epoetins, recording the trade name or the scientific name with the name of the manufacturer." *Id.*

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.[21]

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) 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

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[21] *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).

requiring this — section 351(l)(2) — is unambiguously mandatory.[22] Further, the balance of the scheme imposes obligations on biosimilar applicants and reference product sponsors that flow directly from the provision in question.[23] 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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[22] *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).

[23] *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 quality 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.

Respectfully submitted,

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