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Re: Docket No. FDA-2011-D-0611: Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; 77 Fed. Reg. 8885 (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Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to FDA's issuance of draft guidance for industry entitled "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" ("*Questions and Answers* draft guidance" or the "draft guidance").[1] PhRMA is a voluntary, nonprofit association that represents the country's leading pharmaceutical research and biotechnology companies, which are devoted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to developing, manufacturing, and approving biosimilars, we applaud FDA's decision to seek public input by issuing this draft guidance, as well as two additional draft guidances, on implementation of the BPCIA and considerations relevant to establishing biosimilarity. We are pleased to offer the following comments on the draft guidance, and we hope that FDA will continue to seek stakeholder input openly and transparently as it implements the BPCIA.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. 8885 (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. "Publicly Available" Information

The draft guidance (A.I.13. page 11) indicates that biosimilar applicants may rely on "publicly-available information" regarding FDA's previous determination that a reference product is safe, pure, and potent. The draft guidance states that "publicly-available information" will "generally" include the types of information found in a biologics license application (BLA) action package.[2] The draft guidance further indicates that FDA will publish information on its

[2] An action package includes the following: documents generated by FDA related to review of the application; documents relating to the format and content of the application generated during drug development; labeling submitted by the applicant; "a summary review that documents (continued...)

website about previous determinations for reference products, but that this information may not include all information "that would otherwise be disclosable in response to a Freedom of Information Act request."[3]

While section 351(k)(2) of the PHSA permits a biosimilar applicant to rely on publicly available information regarding the prior approval of the reference product, PhRMA notes that the statute ultimately requires the 351(k) applicant to make a comparative showing of biosimilarity. Specifically, the BPCIA permits FDA to approve a proposed biosimilar product only if the applicant shows that its product is "highly similar" to its reference product and that there are no clinically meaningful differences between the two. This is inherently a comparative showing, supported by comparative information generated and submitted by the biosimilar applicant. PhRMA believes that the contents of the reference product action package, while publicly available, are likely to be of limited relevance to this showing.

Moreover, PhRMA is very concerned about the agency's comment that additional information regarding the review of the innovative product might be disclosable under FOIA. Maintaining the confidentiality of protected, innovator proprietary information is critical to continue to provide incentives for medical innovation, and FDA should do nothing to decrease such incentives to perform resource-intensive research. It is essential as a matter of federal statute, federal constitutional law, and public policy that confidential commercial information and trade secrets submitted by biopharmaceutical companies be protected by FDA and not released, whether in response to FOIA requests or on the agency's website. In particular, release of information beyond what is contained in FDA's action packages (e.g., the basis for approval, a summary of the pertinent clinical trials, and FDA's assessment of the benefits and risks of the product) could cause grave competitive harm to the reference product sponsor. For example, it is possible that released data, or some of these data, could be used to support approval of a full application under section 351(a). These data could also be used to support approval in other countries, even after redaction of trade secret information. At a minimum, the data would provide competitors with insight into how to develop related products, providing research shortcuts that eliminate the first entrant's competitive advantage. Maintaining the confidentiality of protected, innovator proprietary information is critical to continue to provide incentives for medical innovation. Accordingly, if by the final sentence FDA means to signal that it contemplates releasing more information about, or from, reference product applications than currently released in "action packages," PhRMA requests a clear description of the agency's plans and an opportunity to comment further.

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conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrence with review conclusions"; the Division Director and Office Director's "decision document"; and identification by name of each FDA officer or employee who participated in the approval decision and consents to being identified. FDCA § 505(l)(2)(C).

[3] FDA Guidance for Industry, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009," *Draft* (Feb. 2012), at 11 (hereafter the "*Questions and Answers* Draft Guidance").

In light of these concerns, PhRMA also encourages FDA to revise section 601.51 of its regulations ("*Confidentiality of data and information in applications for biologics licenses*"), which has not been updated since the 1970s and does not reflect enactment of the BPCIA. These regulations should be amended to protect innovator data by providing that safety and effectiveness data and information submitted by a reference product manufacturer are confidential commercial information or trade secrets that may not be released by FDA until statutory exclusivity expires (i.e., until 12 years, plus any pediatric exclusivity, after licensure) and *even then* may not be released if extraordinary circumstances exist, meaning if the information in question retains commercial value.

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 (A.II.1, page 12), 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.

D. 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)."[4] 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).[5] 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."[6] 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

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

[5] 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).

[6] *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).

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.

E. 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 draft guidance (A.I.4, page 5) acknowledges and discusses each of these requirements, as well as addresses the extent to which FDA will permit differences in additional product characteristics not expressly mentioned in the statute: delivery devices, container closures, formulation, and presentations.

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.

F. Exclusivity

Section 351(k)(7) of the PHSA provides biological products that are the subject of 351(a) (full) applications with 12 years of exclusivity, subject to a very narrow exception — known as the first licensure provision — for applications filed by certain entities proposing certain modifications to previously licensed products. During this 12-year period, approval of a biosimilar citing that biological product as a reference product may not be made effective. The draft guidance (A.III.1, page 15) instructs sponsors to request exclusivity in their BLAs and

states that this request should "describe how the proposed biosimilar product meets the statutory requirements" and include "data and information" to support the request.[7]

As an initial matter, PhRMA does not support the suggestion that *justification* for exclusivity requests should be necessary. The statute provides 12-year exclusivity presumptively, with a narrow exception that arguably should be invoked *by the agency* and only in certain narrow situations. It does not seem consistent with the statute to require applicants to prove in every case that the exception does not apply. (If the agency expects a justification only in certain cases, more clarity about *when* supporting data and information are required is essential.) Moreover, the draft guidance does not describe the data and information that FDA expects a sponsor to include. A reasonable understanding of the exclusivity that may result is *critical* to investment decisions with respect to new medicines, and we are extremely concerned about the lack of transparency with regard to the rules FDA intends to apply. We strongly request the agency to provide additional clarity on exclusivity requests and supporting "data and information" as soon as possible.

FDA has also remained silent with respect to important questions regarding the exclusivity provision that were clearly raised in the 2010 docket. Because both innovators and biosimilar sponsors must make important investment and development decisions *now*, we believe it is incumbent on the agency to address these issues as soon as possible. We highlight below four issues of particular importance to our members.

First, the first licensure exception to 12-year exclusivity applies to supplements and certain subsequent applications filed by the same company or a licensor, predecessor in interest, or other "related entity." We urge FDA to define "other related entity" as soon as possible — and, in so doing, to adopt an approach that is objective, easy to apply, and consistent with the policy goals of exclusivity. Specifically, as explained in our December 2010 comments, FDA should treat a second applicant as "related" to a previous BLA owner if the two entities are under common ownership and control.[8] We are aware of no evidence that the drafters meant anything other than "related entity" in this ordinary sense. PhRMA also believes that it would be inadvisable for FDA to take any approach requiring it to delve further into the nature and implications of corporate structures and relationships, given the complexity of these relationships, the agency's lack of relevant expertise, and the likelihood that subjective calls in this area would invite lengthy and costly legal disputes that could delay patient access to new therapies.

Second, PhRMA requests that the agency confirm it will take a straightforward and plain language approach to the statutory language in subparagraph (C)(ii)(I) of the first licensure provision. Specifically, *any* modification to the structure of the biological product with a change in safety, purity, or potency should result in a 12-year exclusivity period (for the new

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[7] *Questions & Answers* Draft Guidance, *supra* note 3, at 15.

[8] As we explained in December 2010, the common ownership or control test, or other tests that ask essentially the same question, are widespread in the U.S. legal system. PhRMA, *Comment,* "Approval Pathway for Biosimilar and Interchangeable Biological Products," Docket No. 2010-N0477 (Dec. 23, 2010), at 22.

application). Modifications in structure include changes in amino acid sequence, differences due to post-translational events or infidelity of translation or transcription, and differences in glycosylation patterns or tertiary structure. Also, *any* change in safety, purity, or potency leads, as a matter of law, to a 12-year exclusivity period (for the new application). In our view, the statute does not authorize FDA to impose considerations of clinical superiority or benefit. In any case, where a new application receives its own 12-year exclusivity period, of course, exclusivity on the first licensed product will expire as scheduled.

Third, PhRMA requests that FDA confirm that it intends to follow the umbrella policy with respect to biological product exclusivity. In implementing the new chemical entity (NCE) exclusivity provisions of the Hatch-Waxman amendments, FDA has for years followed an "umbrella policy," pursuant to which a company's subsequent applications for products containing its previously approved NCE are protected until the NCE term expires. As explained in our December 2010 comments, this policy is uncontroversial and has been in place since FDA implemented the Hatch-Waxman amendments, and a review of historical *Orange Books* confirms its consistent (and to our knowledge unbroken) application.[9] In the context of biological products, this would mean that a supplement or subsequent application that was not entitled to its own 12-year period, because of the first licensure exception, would be protected for any remaining period of exclusivity applicable to the first licensed product to which it is related. As the agency noted in 1989 when adopting its NCE regulation, any other approach would seriously undermine the value of exclusivity and incentives to innovate.

Finally, PhRMA requests that the agency commit to providing guidance with respect to eligibility for exclusivity as early as possible during the biological product development process. Where eligibility turns on the relationship between the applicant and an earlier BLA holder, for example, we believe a decision could be made as early as the IND phase. We see no reason for the agency to wait for BLA submission, let alone BLA approval. Where eligibility turns on the final structural characterization of the molecule, it may be necessary in some cases to wait until the BLA has been filed, but we would ask the agency to make a good faith effort to provide an initial answer earlier whenever possible. Development of new biologics is enormously risky, expensive, and time consuming, and lingering uncertainty about the resulting exclusivity may make it difficult to justify the investments needed to bring these medicines to the market.

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.

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[9] *Id.* at 21–22.

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."[10] 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.[11]

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

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[10] FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," *Draft* (Feb. 2012), at 20 (hereafter the "*Scientific Considerations* Draft Guidance").

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

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.

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.[12]

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[12] *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).

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 requiring this — section 351(l)(2) — is unambiguously mandatory.[13] Further, the balance of the scheme imposes obligations on biosimilar applicants and reference product sponsors that flow directly from the provision in question.[14] 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

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[13] *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).

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

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*.

IV. Conclusion

PhRMA appreciates FDA's issuance of draft guidance to provide proposed answers to questions regarding implementation of the BPCIA 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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