PhRMA

December 23, 2010

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

Re: Docket No. 2010-N-0477: Approval Pathway for Biosimilar and Interchangeable Biological Products; 75 Fed. Reg. 61497 (Oct. 5, 2010)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to FDA's request for comment entitled "Approval Pathway for Biosimilar and Interchangeable Biological Products."[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 2009, the biopharmaceutical industry invested more than $65 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 also applaud FDA's decision to begin implementation of the BPCIA with a Part 15 hearing and the opening of a public docket for stakeholder comment. PhRMA was pleased to participate in the hearing, and we offer these written comments to supplement the oral testimony we provided on November 3. Given the complexity of the issues involved in developing, manufacturing, and approving biosimilars, we hope that FDA will continue to seek stakeholder input openly and transparently in order to best protect patients and to ensure implementation is based on sound science.

I. Introduction and Summary

FDA's implementation of the BPCIA should be informed by the agency's overall mission, which is both to promote the public health (and thus adopt policies that encourage innovation as well as policies that allow appropriate abridgment of marketing applications and practices that enable swift application review) and to protect the public health (and thus ensure that all human medicines are safe and effective).[2] As explained

[1] 75 Fed. Reg. 61497 (Oct. 5, 2010).

[2] *See* 21 U.S.C. § 393(b).

by PhRMA on November 3, implementation of the statute should be guided by three general principles. First, FDA should ensure that patients have access to safe and effective biosimilars. Second, the pathway to market for biosimilars should be based on sound science and should be developed through an open and transparent process. Third, FDA should encourage continued medical innovation and implement policies that enable innovative competition.

Guided by the agency's mission to protect patient safety in its approval of biosimilar products and by the general principles described above, PhRMA recommends that FDA:

- **Require Clinical Trials to Demonstrate Biosimilarity.** After completion of appropriate analytical and preclinical studies establishing molecular similarity and similar preclinical properties, each biosimilar applicant should be required to compare the proposed biosimilar to the reference product in at least one clinical trial involving the reference product. Given the limits of current scientific knowledge and for reasons of patient safety, PhRMA cannot envision a biosimilar product or class of products for which comparative clinical studies would be unnecessary for approval.

- **Exercise Caution with Respect to Interchangeability Determinations.** There is currently no scientific, regulatory, or medical consensus regarding the data that would meet the statutory standard for interchangeability. If at some point FDA decided that interchangeability determinations were scientifically feasible, the agency would need to consider the possibility that the reference product and the interchangeable biosimilar would diverge once the biosimilar was deemed interchangeable. FDA would also need to address how the subsequent approval of new indications for a reference product would affect a biosimilar's interchangeability status, particularly if the new indications did not have the same mechanism of action as the previously approved indications.

- **Require Unique Product Names to Ensure Meaningful Pharmacovigilance.** When a patient or healthcare professional reports an adverse event associated with a biologic, it will be essential to know exactly which product the patient was receiving. Unique product names are the best way to accomplish this, and FDA should ensure that each biosimilar's labeling and packaging bears a nonproprietary name that differentiates it from the reference product and other biosimilars.

- **Require that Biosimilarity be Proven by Analytical, Preclinical, and Clinical Data from Comparisons with a U.S.-Licensed Biologic.** To be approved under the BPCIA, a biological product must

be biosimilar to a single FDA-approved reference product. Any data comparing the biological product instead to a foreign product may be used only to corroborate the pivotal data from comparisons with the U.S.-licensed reference product. They may never be the sole basis of approval of the biosimilar.

- **Maintain the Distinction Between BLAs and Biosimilar Applications.** FDA should articulate and maintain the clear distinction between biologic license applications (BLA) filed under section 351(a) of the Public Health Service Act (PHSA) and applications filed under section 351(k) (biosimilar applications). 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 — i.e., that the section requires original applications demonstrating product safety, purity, and potency. It would upset the careful balance struck by Congress between biosimilar market entry, 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 findings, prior approvals, or previously submitted data without consent. The agency should make it clear that section 351(k) is the only pathway available for licensure of products that rely without consent on previously submitted data or approvals.

- **Require Compliance with Section 351(l).** FDA should ensure that the BPCIA functions as intended, so that biosimilar applicants may avoid performing the full preclinical and clinical testing that is required for a section 351(a) application and innovators receive data exclusivity and a meaningful opportunity to litigate patent infringement issues prior to biosimilar market entry. FDA should therefore require that each biosimilar applicant include with its application a certification that it will, within 20 days after notification has been received that the application was accepted for review, 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.

We offer below our detailed responses to the specific questions asked by FDA in the October 5 *Federal Register* notice. PhRMA also recommends that FDA study the views and experiences of the World Health Organization (WHO), the European Medicines Agency (EMA), and the various individual countries that have already established policies and guidance on the approval of biosimilars.

II. Response to FDA's Questions

A. Biosimilarity

1. What scientific and technical factors should the agency consider in determining whether the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components?

Given the complexity of biologic molecules and FDA's need to ensure that approved biosimilar products are safe and effective, establishing biosimilarity should consist of a stepwise process that begins with molecular evaluations and ends with clinical trials comparing the safety and efficacy of the reference product and the proposed biosimilar. The first step in the process is the analytical characterization of the physiochemical properties and biological activities of both the reference product and the proposed biosimilar. If a reference product or proposed biosimilar cannot be adequately characterized using existing analytical techniques, the applicant would generally be unable to make any meaningful comparative characterization. In this case, the proposed biosimilar should not be approved using the section 351(k) pathway.

Next, a biosimilar applicant should use comparative analytical evaluations of the U.S.-licensed reference product and the proposed biosimilar to establish a high degree of molecular similarity between the two products.[3] At a minimum, FDA should require biosimilar applicants to make two showings in order to satisfy the high degree of molecular similarity standard. First, the reference product molecule and the proposed biosimilar molecule should have an identical amino acid sequence. Amino acid sequence is a controllable characteristic of a molecule and should therefore be preserved in a proposed biosimilar in all cases. Differences in certain N- or C- terminal post-translational modifications, such as prenylation and palmitoylation, should not preclude a finding of molecular similarity, if the biosimilar applicant establishes with further analytical evaluations and preclinical and clinical data that they have no effect on the safety or efficacy of the proposed biosimilar.

Second, the molecules should have higher order structures and post-translational modifications that are as similar as possible. The meaning of "as similar as possible" will vary based on the capacity of science and technology at any given time. Nonetheless, FDA should require a biosimilar applicant to demonstrate that the higher order structures of the molecules are as similar as is feasible under current science. Again, certain differences in post-translational modifications such as glycosylation should not prohibit a finding of molecular similarity. But a biosimilar applicant should demonstrate which structures affect the function of the reference product molecule and that these structures have been preserved in the proposed biosimilar. If they have not been preserved, additional comparative analytical, preclinical, and clinical studies will be

[3] While the BPCIA allows FDA to approve biosimilar applications based upon any product licensed under section 351(a), we are focusing in our comments on biosimilar therapeutic protein products.

needed to demonstrate that the structural differences do not significantly influence the function of the molecule or have any effect on dosing, immunogenicity, or clinical outcomes.

2. What scientific and technical factors should the agency consider in determining the appropriate analytical, animal, and clinical study or studies to assess the nature and impact of actual or potential structural differences between the proposed biosimilar product and the reference product?

Throughout the biosimilar development and approval process, the quality and scientific standards employed by the biosimilar applicant and FDA must be as sensitive and sophisticated as those used for any new biological product. In some cases, the chemistry, manufacturing, and controls (CMC) standards for the proposed biosimilar will need to be more stringent than those for the reference product. For example, if a reference product sponsor makes a manufacturing change during clinical development, this change can be evaluated throughout its clinical program. Biosimilar applicants, however, will generally perform abbreviated clinical testing, which may not permit an adequate evaluation of any changes. Moreover, the scope and nature of the clinical program will be based in part on the findings in the comparative analytical studies. Manufacturing changes subsequent to these analytical studies could render those findings obsolete and the abbreviated clinical program insufficient to satisfy the biosimilar approval standard. FDA should therefore exercise caution with respect to manufacturing changes implemented by biosimilar applicants once clinical testing has begun.

FDA should require the use of multiple orthogonal methods, including mass spectrometry and chromatography, to detect structural differences between the reference product and the proposed biosimilar. Any single measure would not be sufficient to establish with certainty the differences between the products. These analytical methods must together be sufficiently sensitive to detect any differences between the products. Although these methods will change based on the molecule at issue and as the science evolves, FDA should ensure that biosimilar applicants are adapting to the changing science by employing state-of-the-art analytical techniques.

Once a biosimilar applicant has adequately compared the reference product and the proposed biosimilar at the quality level, it should compare the properties of the products in appropriate preclinical *in vivo* and *in vitro* studies. These studies should be designed not only to determine whether the products have different biological or pharmacodynamic activity, toxicological properties, or other characteristics, but also to measure whether any structural differences noted at the quality level have an effect on preclinical properties. Any differences identified in preclinical testing must be thoroughly explored in the clinical program. Some differences may be so significant that an ordinary (non-abbreviated) preclinical program is warranted before testing in humans would be appropriate. And some may be so significant that continued use of the biosimilar pathway is inappropriate.

After completion of appropriate analytical and preclinical studies establishing a high degree of molecular similarity and highly similar preclinical properties, the biosimilar applicant should be required to compare the proposed biosimilar to the reference product in at least one clinical trial involving the U.S. reference product. These clinical trials should generally use clinical efficacy endpoints that were the same as those for the reference product's trials. FDA should, however, require biosimilar applicants to use endpoints that are the most sensitive to detecting differences between the reference product and the proposed biosimilar.[4] This may mean that in some cases the endpoints used in the proposed biosimilar's clinical trials differ from those used in the reference product's pivotal trials. And, in some cases, the most sensitive endpoints will not be clinical efficacy, but surrogate or pharmacodynamic, endpoints. For example, the EMA guidance for human insulin biosimilars recommends that sponsors primarily use pharmacodynamic and pharmacokinetic data from clinical trials to determine whether the product can be authorized.[5] In 2008, the EMA determined that three proposed human insulin biosimilars were not approvable. One of the primary concerns was that, contrary to EMA guidance, the sponsor had not completed any pharmacokinetic clinical trials. The sponsor also attempted to rely on clinical efficacy trials when its pharmacodynamic data produced unreliable and unfavorable results. This strategy failed "because it is evident that clinical endpoints being less sensitive, it cannot compensate for the failure to show pharmacodynamic similarity."[6] Where pharmacodynamic or surrogate endpoints are used, they must be validated in order to establish that they correlate with clinical outcomes, and it may be appropriate to use the reference product's clinical outcome endpoints as secondary endpoints.[7]

FDA should generally require that these clinical trials employ equivalence designs rather than non-inferiority designs because the BPCIA requires that there be no

[4] EMA guidance recognizes that clinical trials should be designed using methods sensitive enough to detect differences between the proposed biosimilar and the reference product. *See, e.g.*, EMA Committee for Medicinal Products for Human Use, Guideline on Non-clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Erythropoietins 6 (2010) (stating that "the fact that epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin-related endpoints to detect possible differences in the efficacy of the treatment arms. Therefore, epoetin dosage should be a co-primary endpoint in both" the correction phase study and the maintenance phase study).

[5] EMA Committee for Medicinal Products for Human Use, Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin 4-5 (2006).

[6] EMA, Withdrawal Assessment Report for Insulin Human Rapid Marvel 16 (Feb. 21, 2008), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067086.pdf.

[7] EMA Committee for Medicinal Products for Human Use, Draft Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies 9 (2010) ("For most of the clinical conditions that are licensed for mAbs, specific CHMP guidance on the clinical requirements exists. However, to establish biosimilarity, deviations from these guidelines (choice of endpoint, timepoint of analysis of endpoint, nature or dose of concomitant therapy, etc) may be warranted. Such deviations need to be fully scientifically justified. In such circumstances it is recommended, where feasible, to include the usually recommended endpoints for a certain condition as secondary endpoint.").

meaningful differences between the reference product and proposed biosimilar. Equivalence trials permit a more robust comparison of the efficacy of the reference product with the efficacy of the proposed biosimilar. As explained by the WHO, "equivalence trials are clearly preferable to ensure that the [biosimilar] is not clinically less or more effective than the [reference product] when used at the same dosage(s)."[8] The use of both upper and lower margins will reveal both decreased and increased efficacy of the proposed biosimilar relative to the reference product. These margins must be pre-specified and should be selected based on the largest difference in efficacy that is considered to have no clinical relevance — i.e., that would not matter in clinical practice.[9] A proposed biosimilar that is shown to have a level of efficacy outside the upper equivalence margin should be the subject of a BLA submitted under section 351(a) given the uncertain impact that increased efficacy can have on dosing, immunogenicity, and other safety issues. Equivalence trials are also preferable because they are generally larger than other types of trials, thus permitting a biosimilar applicant to provide more safety data for FDA review prior to approval.

The approval of a biosimilar could, however, be supported by non-inferiority trials in certain narrow circumstances. For example, if the biosimilar applicant can establish that there is no clinical advantage or disadvantage from an increased dose (i.e., the product pharmacodynamically saturates the target at a given level), a non-inferiority trial could be scientifically appropriate. But the biosimilar applicant must meet the burden of demonstrating that a non-inferiority trial is acceptable. In addition, because non-inferiority trials are typically smaller in size, the biosimilar applicant may not be able to gather sufficient safety data for approval from non-inferiority efficacy trials alone.

The size of the proposed biosimilar clinical program will vary by product and by product class. FDA should consider, at a minimum, the size of the reference product's pivotal trials, the extent of molecular differences revealed by the biosimilar applicant's analytical evaluations, and the size of the disease population (i.e., a larger disease population would more easily permit a larger biosimilar clinical trial).

In the Appendix to these comments, PhRMA provides concepts to consider in the design and conduct of biosimilar preclinical and clinical programs.

3. What range of structural differences between a proposed biosimilar product and the reference product is consistent with the standard "highly similar" and may be acceptable in a 351(k) application if the applicant can demonstrate the absence of any clinically meaningful differences between the proposed biosimilar product and the reference product?

[8] WHO, Expert Committee on Biological Standardization, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) 22 (2009).

[9] *Id.*

The demonstration of a high degree of molecular similarity should always be a prerequisite to use of the section 351(k) abbreviated pathway. As mentioned above in response to question II.A.1, the reference product and the proposed biosimilar should have an identical amino acid sequence. The products should also have higher order structures and post-translational modifications that are as similar as possible. If a biosimilar applicant cannot make these analytical showings, it should not be permitted to use the abbreviated pathway because the differences between the products would warrant a BLA to fully address the unique clinical profile of the proposed biosimilar. Whatever minor structural differences FDA permits, these differences must be shown with comparative preclinical and clinical data to have no effect on product safety or efficacy.

4. Under what circumstances should the agency consider finding that animal studies or a clinical study or studies are "unnecessary" for submission of a 351(k) application?

Given the limits of current scientific knowledge and the need to protect patient safety, PhRMA cannot envision a biosimilar product or class of products for which comparative clinical studies would be unnecessary for approval. Because a biosimilar is similar, not identical, to a reference product, a proposed biosimilar cannot be assumed to have the same clinical profile as the reference product. Comparative analytical data are not sufficient to ensure that these complex molecules have similar clinical safety and efficacy profiles. Although physiochemical analytical techniques are increasingly sensitive at detecting differences, the corresponding ability of scientists to link differences in structure to differences in clinical outcomes remains limited. FDA therefore must require at least one comparative clinical trial prior to approval. The preclinical and clinical programs for a proposed biosimilar may, however, be abbreviated in comparison to the lengthy research and development process that culminates in a BLA. For example, a biosimilar applicant would probably not need to produce as significant an amount of animal data as the reference product sponsor. Nor would it generate as many Phase I or Phase II data. To the extent FDA waives clinical data requirements for a particular proposed biosimilar, it must consider the safety risks involved in its decision, with a particular focus on the risk of immunogenicity produced by the proposed biosimilar. In any case, some comparative preclinical data and at least one comparative clinical trial in the nature of a Phase III trial will be essential to ensure that the product is safe, effective, and biosimilar to the reference product.

FDA should generally require a biosimilar applicant to provide clinical data supporting every indication of the biosimilar. Waiving clinical data for a subsequent indication once biosimilarity has been proven with respect to a first indication ("extrapolation") should be permitted only with extreme caution. For example, biosimilar applicants should not be allowed to extrapolate if the indications do not share the same molecular mechanism of action or if the mechanism of action is not well understood. Even if the mechanisms of action are the same and well understood, FDA may need to consider other factors, such as whether the mechanisms of disease are the same, whether the indications share the same patient disease state (e.g., immuno-competent, immuno-suppressed, etc.) and population, the quality and amount of data that

have been provided to support the first indication, whether the indications have similar risk/benefit ratios, whether the indications share the same route of administration, and the extent of comparative characterizations of the molecules using current analytical methods. Extrapolation from an indication that has a high risk/benefit ratio to an indication that has a low risk/benefit ratio would likely be more scientifically justified than extrapolation from an indication with a low risk/benefit ratio to an indication with a high risk/benefit ratio.

A few commentators, including one at the Part 15 hearing on November 2, have questioned the ethical implications of biosimilar clinical trials. They focus on Article 20 of the Declaration of Helsinki, which states, in part, that "[p]hysicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results." They suggest that requiring clinical testing of biosimilars will violate this article, and other ethical principles related to clinical trials, because these trials are duplicative of the clinical program for the reference product. This is incorrect. Biosimilar clinical trials are comparative — i.e., they are designed to demonstrate that the proposed biosimilar is "highly similar" to the reference product and that there are "no clinically meaningful differences" between the products. And ultimately they are intended to facilitate the very thing that these commentators seek: permission to avoid — for a new medicine that is not identical to any other product on the market — a lengthy stand-alone clinical program that would otherwise be needed for approval under section 351(a). PhRMA is aware of no country that interprets the Declaration of Helsinki to require a biosimilar applicant to skip this necessary comparative testing. Doing so would not only contradict Congressional intent as expressed in the BPCIA (and other FDA laws requiring drugs and biologics to be shown to be safe and effective before marketing), but would also expose patients to potentially unsafe and ineffective biological products.[10]

B. Interchangeability

1. What factors should the agency consider in determining whether a proposed interchangeable biological product can be "expected to produce the same clinical result as the reference product in any given patient?"

In order to protect patients who might be prescribed biologics for which there are interchangeable biosimilars, Congress intended the interchangeability standard to be an exceptionally high standard that could be met only with an additional showing

[10] To the extent these commentators instead object to the concept of data exclusivity itself, the issues they raise are outside the scope of FDA's implementation process. But PhRMA vigorously opposes any assertion that data exclusivity raises ethical issues. Data exclusivity does not *require* duplicative testing. Instead, it *precludes* reliance on clinical data for a fixed but finite period of time in order to encourage continuing innovation in new medicines for patients. Data exclusivity appears also in the U.S. generic drug approval laws, it appears in medicines laws around the world, and it is required by various international treaties to which the United States is a party.

beyond that which is required to establish biosimilarity. PhRMA does not believe that this high standard can be met given the current state of the science.

When Congress created the small molecule generic drug approval pathway, the science at the time was generally capable of demonstrating the therapeutic equivalence of a generic drug. Under FDA rules in place prior to 1984, which had been developed through a robust public process and reflected considerable input from the medical and scientific communities, one small molecule drug would be deemed therapeutically equivalent to another if the two were bioequivalent (i.e., the rate and extent of absorption of the active ingredient of one drug did not significantly differ from the rate and extent of absorption of the active ingredient of the other drug) and pharmaceutically equivalent (i.e., they had the same active ingredient, dosage form, route of administration, and strength or concentration).[11] These aspects, particularly sameness of active ingredient, were capable of measurement when the statutory small molecule generic pathway was created. The automatic substitution of generic drugs that resulted under the law of many states from a therapeutic equivalence rating by FDA was therefore grounded in established science. In contrast, there is currently no scientific, regulatory, or medical consensus regarding the data needed to show that a proposed biosimilar can be expected to produce "the same clinical effect in any given patient" — the statutory standard for biological product interchangeability.

If at some point FDA decided that interchangeability determinations were scientifically feasible and that it could define the data needed, the agency would need to address at least two critical issues. First, FDA would need to consider the possibility that the reference product and interchangeable biosimilar would diverge once the biosimilar was deemed interchangeable. In other words, one or both products could "drift" due to changes in manufacturing or other processes. FDA would therefore need to address how an interchangeability determination could be maintained throughout a product's lifecycle. Second, when making an interchangeability determination, FDA would need to keep in mind the potential for a proliferation of relevant biosimilarity and interchangeability relationships. Specifically, there could be multiple similar reference products (possibly with similar names) and multiple biosimilar products for each reference product, and only some of these biosimilar products might be interchangeable with its reference product. FDA would need to be mindful of distribution, prescribing, dispensing, and administration practices and potential impact on patients in such a confused marketplace.

PhRMA believes that deeming a biosimilar interchangeable with respect to a subset of the reference product's approved indications would hopelessly compound this confusion. When a physician or other healthcare professional prescribes a biologic, the dispensing pharmacy typically does not know for which indication the biologic was prescribed. And the burden should not be placed on patients to know this information. If the approved biosimilar has been found interchangeable for some indications but not others, the dispensing pharmacist will not know whether substitution is safe and

[11] *See* FDA, Office of Generic Drugs, Approved Drug Products with Therapeutic Equivalence Evaluations iii-v (2010).

appropriate. The result could be both inappropriate substitution (when the biosimilar is not interchangeable for the indication) and unnecessary avoidance of substitution (when the biosimilar is in fact interchangeable for the indication). For this reason, we believe that biosimilars should not be designated interchangeable unless they are, in fact, interchangeable with respect to every reference product indication.[12]

Interchangeability showings should be made on an indication by indication basis and should be supported by clinical data for each indication, including: (1) indications initially supported by extrapolated data for the purpose of biosimilarity, and (2) indications for which the reference product gained approval after approval of the biosimilar. Analytical data alone would be insufficient to ensure that a biosimilar substituted without the intervention of a healthcare professional would generate no difference in clinical result. FDA would also need to consider how the subsequent approval of new indications for a reference product would affect a biosimilar's interchangeability determination, particularly if the new indications did not have the same mechanism of action as the previously approved indications.

FDA should not waive any application element (i.e., analytical data, animal data, or clinical data) if the biosimilar applicant seeks an interchangeability determination at the time of initial approval of the biosimilar. Moreover, FDA should not make interchangeability decisions at the time of initial approval of the biosimilar product unless the data supporting interchangeability are particularly compelling. Postmarket experience in a large patient population is critical to revealing whether a biosimilar is producing the same clinical result as the reference product, especially with regard to rare immunologically mediated events.

2. What factors should the agency consider in evaluating the potential risk related to alternating or switching between use of the proposed interchangeable biological product and the reference product or among interchangeable biological products?

Interchangeability designations for products intended to be administered more than once require a particularly rigorous showing. This is appropriate because of the difficulty of achieving effective pharmacovigilance of multiple-use biosimilars that are deemed interchangeable. A particular adverse event could be the result of a reaction to an attribute of an individual biosimilar product or a reaction to having switched from one biosimilar to another or from the reference product to a biosimilar or vice versa.

The biosimilar applicant must conduct clinical trials designed to show that switching between the reference product and the biosimilar does not increase the risk to

[12] While a biosimilar applicant may not be able to label its product for the reference product indications as to which there is patent protection, PhRMA believes that the U.S. patent laws would permit the applicant to submit data establishing interchangeability and that patient safety compels this showing before an interchangeability designation is made. *See* 35 U.S.C. § 271(e)(1). FDA will also need to consider the possibility that carving out protected information (including indications) has impermissible patient safety implications.

patients. Special consideration should be given to the sample size, the frequency of switches, the length of any wash-out periods between switches, and the overall length of the study. These trials must also address the potential for increased immunogenicity that can result from switching itself.

Sponsors and FDA must also consider the potential safety implications raised by these trials. Because the risk of switching biological products will be unknown at the outset of a particular trial, for example, only a few patients should be initially included in any switching study. Also, some patients could develop antibodies as a result of the trial that would limit their therapeutic choices after the trial is completed. This, too, will need to be taken into account.

C. Patient Safety and Pharmacovigilance

1. What factors unique to proposed biosimilar or interchangeable biological products and their use should the agency consider in developing its pharmacovigilance program for such products?

In developing pharmacovigilance standards for biosimilars, FDA should consider the pharmacovigilance commitments of reference product sponsors as well as the agency's own infrastructure and its ability to adapt to the unique pharmacovigilance concerns raised by biosimilars. Any biosimilar pharmacovigilance plan should take account of the characteristics of the individual biosimilar, including the extent to which immunogenicity concerns have been addressed in premarket testing; the characteristics of the class to which the biosimilar belongs; any knowledge that the agency and other stakeholders have gained about the reference product and the reference product class since approval of the reference product; and the need for communication from biosimilar applicants and the agency in order to educate healthcare professionals, patients, and other stakeholders on biosimilar pharmacovigilance issues.

Each of these factors takes on even more importance once FDA makes an interchangeability determination. Unique pharmacovigilance standards may need to be developed for interchangeable biosimilars, and FDA should not assume that a pharmacovigilance system adequate for non-interchangeable biosimilars will address all of the safety risks raised once it begins making interchangeability determinations.

FDA should also consider how it can work with other federal agencies to support pharmacovigilance. For example, FDA should encourage the Centers for Medicare and Medicaid Services (CMS) to place a biosimilar in a separate J (billing) code from its reference product, because using the same billing code for both products could impede FDA efforts to collect safety information regarding biosimilars. For instance, FDA's Sentinel Initiative uses unique billing codes to gather safety information about drugs and biologics. If a biosimilar is placed in the same billing code as the reference product, the safety signals of the biosimilar will be indistinguishable from the safety signals of the reference product.

2. What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?

Biosimilar products, like all other new medicines, should be subject to robust pharmacovigilance and, where warranted, robust postmarket commitments to protect patient safety. FDA has the same authority to impose postmarket commitments on biosimilar applicants as it does to impose postmarket commitments on section 351(a) applicants. And scientifically sound use of this authority requires every postmarket scheme to be tailored to the particular risk and benefit profile of the product at issue. PhRMA believes that in general, where a reference product is subject to a risk evaluation and mitigation strategy (REMS), the biosimilar product should have a REMS that is at least as rigorous. In light of the differences between the products (some of which may be unknown due to the abbreviated premarket program for the biosimilar), sound science and patient safety may require that the biosimilar REMS be more extensive. In some cases the postmarket study commitments of a biosimilar sponsor also may be more extensive than those of the reference product sponsor, given the abbreviated preapproval clinical program and the likely need to gather additional postmarket data, including immunogenicity data. Additional postmarket requirements would be appropriate, for example, if the biosimilar applicant extrapolated data to support some indications of the biosimilar. In other cases, the postmarket studies may be less extensive.

An important way to ensure robust pharmacovigilance of biosimilar products and to protect patient safety is to require that biosimilars have unique names. When a patient or healthcare professional reports an adverse event associated with a biologic, it will be essential to know exactly which product the patient was receiving, as well as from which products the patient may have recently been switched.[13] Unique product names are the best way to accomplish this.[14] National drug codes (NDCs) and lot

[13] *See, e.g.*, EMA Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products 4 (2005) ("It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.").

[14] The recent 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

numbers are helpful, but cannot ensure the same level of pharmacovigilance because patients and healthcare professionals will not as readily have access to this information and because both prescribing and adverse event reporting are 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. And they will help facilitate recalls and appropriate reimbursement policies.

For these reasons, PhRMA believes 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 is not clear at present 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 reference products and other biosimilars, while others will have different names.[15]

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. As explained above in the answer to question II.B.1, PhRMA believes that interchangeability determinations are not scientifically possible at this time and, in any case, should be made only after a sufficient postmarket immunogenicity database has been accumulated. Changing an approved biosimilar's nonproprietary name after it was deemed interchangeable would create confusion, so the same naming convention (i.e., unique nonproprietary names) should be applied to interchangeable biosimilars.

3. If each product were given a unique nonproprietary name, should a distinguishing prefix or suffix be added to the nonproprietary name for a related biological product that has not been demonstrated to be biosimilar, a biosimilar product, or an interchangeable product to facilitate pharmacovigilance? What factors should be considered to reduce any negative impact on the healthcare delivery system related to unique nonproprietary names for highly similar biological products?

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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*.

[15] Each of the fourteen biosimilars approved to date in Europe has been distinguishable, although some have the same non-proprietary name. For example, five biosimilar applications have been approved based on the reference product Eprex (epoetin alfa): Binocrit (epoetin alfa), Epoetin alpha Hexal (epoetin alfa), Abseamed (epoetin alfa), Retacrit (epoetin zeta), and Silapo (epoetin zeta).

Given the safety and pharmacovigilance issues described above, PhRMA supports the use of unique nonproprietary names for biosimilars, whether or not these biosimilars have been deemed interchangeable. The nonproprietary names for biosimilars and their reference products should have common stems but different suffixes or prefixes. This naming convention will help ensure adequate pharmacovigilance of biosimilars; the common stem ensures that a reference product and a biosimilar are recognized as related products and permits trends applicable to all of these products to be recognized, and the suffix or prefix permits problems applicable to a specific product to be distinguishable. PhRMA also believes that physician, pharmacist, and patient confusion will be best managed if unique names are established prior to market entry and not modified later (for example, upon a showing of interchangeability).

The risk of patient confusion caused by unique names is small because biologics are often administered in close contact with healthcare professionals. And this risk is significantly less than the safety risk posed to an individual patient by inappropriate automatic substitution or the safety risk to the broader patient population by the inability to adequately track safety signals. The use of common stems will also help reduce any confusion regarding whether a patient is receiving a type of therapy. Moreover, any patient or healthcare professional confusion caused by unique names can be addressed by clear communication and educational programs by biosimilar applicants, reference product sponsors, and the agency as well as by detailed labeling for biosimilars, as discussed in more detail below.

4. What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent unsafe substitution of biological products?

FDA can most effectively prevent inappropriate substitution by ensuring that biosimilar products have unique nonproprietary names. This should help to prevent the automatic substitution of biosimilars that have not been found by FDA to be interchangeable. This in turn may help to prevent the potentially serious clinical problems that could result if a non-interchangeable product were dispensed to a patient without the knowledge of the treating physicians.[16]

As part of its implementation of the BPCIA, FDA should educate healthcare professionals, including prescribers and pharmacists, about the statute and, in particular, the limitations of a biosimilarity finding and the differences between biosimilarity and interchangeability. FDA should also issue a policy statement that unless it has deemed a biosimilar interchangeable with a prescribed product, that

[16] EMA, Questions and Answers on biosimilar medicines (similar biological medicinal products) (Oct. 22, 2008), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf ("Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.").

biosimilar should not be substituted for the prescribed product without the express consent of the prescribing physician. FDA should communicate this policy statement clearly in the labeling for biosimilars, on the agency's website, and in letters to healthcare professionals, pharmacies, formularies, and states.

5. What are some mechanisms that FDA may consider to communicate findings that a particular product is or is not biosimilar to or interchangeable with a given reference product?

FDA should primarily communicate information about each biosimilar to patients and healthcare professionals in the product's labeling. Unlike generic small molecule drugs, biosimilar biologics will not be the same as their reference products and will require unique labeling. This labeling should clearly state that the product is a biosimilar, which indications were supported by clinical data and which were based on extrapolation, how many (and what sort of) clinical data supported its approval, and which product served as the reference product. The labeling of a biosimilar should also prominently state that FDA has not deemed the product interchangeable (unless the agency has done so) and that a non-interchangeable biosimilar should not be substituted for the prescribed product without the express consent of the individual treating healthcare professional. FDA may find it helpful to refer for guidance to the current labeling of insulin products, which generally states that any change in brand should be made cautiously and only under the supervision of a physician.

FDA will also need to set a policy with respect to indications added to reference product labeling after approval of biosimilars. PhRMA believes that the labeling of already marketed biosimilar products should be updated promptly to disclaim new indications unless and until supporting data (or justification for extrapolation) have been approved by FDA. In the case of an interchangeable biosimilar, as noted above in response to question B.1, extrapolation should not be permitted.

As noted above, the labeling should be the primary means of communication about biosimilars; if FDA chooses to communicate information about interchangeability designations in another setting (for example, a website list of approved biosimilars), it should be careful to differentiate between interchangeable biosimilars and other biosimilars. Agency communications must also differentiate between biosimilar indications as to which a clinical showing was made and indications as to which extrapolation was permitted. Unique nonproprietary names will somewhat reduce the confusion regarding the relationships between reference products, biosimilars, and interchangeable biosimilars, but PhRMA believes that sophisticated and carefully detailed communication by the agency will nevertheless be required. FDA should consider using any agency communication as an opportunity to educate healthcare professionals, pharmacies, formularies, and states about the meaning of biosimilarity and interchangeability.

D. The Use of Supportive Data and Information

1. From a scientific perspective, to what extent, if any, should animal or clinical data comparing a proposed biosimilar product with a non-U.S.-licensed comparator product be used to support a demonstration of biosimilarity to a U.S.-licensed reference product? What type of bridging data or information would be needed to scientifically justify the relevance of the comparative data?

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)."[17] 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).[18] 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."[19] 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 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. These data should 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 foreign innovator product should have the same drug substance, same dose, dosage form, and route of

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

[18] The patent and data exclusivity provisions of the BPCIA also clearly indicate 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).

[19] *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).

administration as the U.S. reference product. It should also 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, we believe 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.

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. They may 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 reference 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 be approvable standing alone without any additional foreign data, and FDA should always require that a proposed biosimilar satisfy the statutory standard for approval with data from comparisons to a U.S. reference product.

E. The Definition of a Biological Product

1. What scientific and technical factors should FDA consider if it develops a regulatory definition for the category of ''protein'' (as distinguished from peptide or polypeptide)?

2. *What scientific and technical factors should FDA consider if it develops a regulatory definition for the category of ''any chemically synthesized polypeptide''?*

FDA has asked two questions with respect to the new definition of "biological product." PhRMA is answering both questions together. As amended by Congress, section 351(i) of the PHSA now states that a biological product includes any "protein (except any chemically synthesized polypeptide)." FDA has asked, in essence, what constitutes a protein and how the agency should identify "chemically synthesized" polypeptides. PhRMA believes that the distinction between protein and polypeptide is ambiguous, insofar as both proteins and polypeptides involve chains of amino acids. PhRMA also believes that the phrase "chemically synthesized" may be deceptively simple, insofar as some portions of a particular manufacturing process may involve biosynthesis while others involve chemical synthesis. We urge the agency to adopt a more nuanced and functional approach to the new provision. Specifically, PhRMA proposes that if the function of a polypeptide depends on its higher order (secondary, tertiary, quaternary) structure, that polypeptide should be regulated under the PHSA and not under the Federal Food, Drug, and Cosmetic Act (FDCA).

F. Guidances

1. What types of guidance documents for industry should be a priority for the agency during the early period of implementation?

PhRMA applauds FDA's decision to begin implementation of the BPCIA with a Part 15 hearing and the opening of a public docket for stakeholder comment. We believe that the agency should implement the BPCIA in an open and transparent manner that facilitates the timely participation of all stakeholders who can contribute to ensuring the safety, efficacy, and timely market entry of biosimilars. For this reason, PhRMA strongly urges FDA to issue general and class-specific guidance in accordance with section 701(h) of the FDCA, and (as warranted) generally applicable biosimilar regulations.[20] Although a guidance development process will consume both time and resources, it should not slow the approval of biosimilars. The European experience has shown that guidance can be finalized within 12 to 18 months, and we believe that FDA can take advantage of the EMA's learning (i.e., saving time) with respect to both general scientific issues and product classes that are likely to be the first under consideration.

The EMA's three-step process for guidance development has been successful and, in the United States, could be easily reconciled with the requirements of section 701(h) and FDA's good guidance practice (GGP) regulations.[21] The EMA first issues a concept paper setting forth the topics to be covered in the guidance and any critical issues that need to be addressed. The EMA releases this concept paper for public comments. Next, after analyzing the public comments, the EMA publishes a draft guidance and again seeks public comment on the document. Last, the EMA finalizes the guidance. This process permits significant public comment and agency consideration, but has not unduly delayed patient access to biosimilars.

Although the adoption of guidance will require an up-front investment of agency time and resources, PhRMA believes it will lead to a more efficient process over the long term and ultimately conserve agency and applicant time and resources. For example, the process will allow the agency and scientific community to focus on and resolve — up front — issues that will be common to a product class, which will benefit all applicants in the class. Opportunities for public comment permit reference product sponsors, who have critical insight into biologic product characteristics and manufacturing processes, to help inform the standards that will be used. Innovators, payors, healthcare professionals, patients, and pharmacies will have a meaningful opportunity to provide input with respect to both scientific standards and pragmatic issues raised by biosimilars. A transparent and participatory process should help to ensure that

[20] Although FDA's *Federal Register* notice did not raise the question of rulemaking, PhRMA believes that some of the agency's regulations will need to be reconsidered in light of the BPCIA and that regulations will be appropriate for certain new issues. For example, the agency's FOIA regulations will need to be revised to account for the new approval pathway. And regulations governing the format and content of biosimilar applications, similar to those in place for the format and content of BLAs, would be appropriate.

[21] 21 C.F.R. § 10.115.

the agency's final scientific conclusions achieve widespread acceptance. And guidances allow FDA to be flexible; the agency can set forth general principles, but retains the right to modify the guidance or to impose different requirements on a particular product or product class.

Some of the burden associated with adopting general and class-specific guidance could be alleviated if FDA were to form an advisory committee or group of advisory committees to assist in BPCIA implementation. A committee could — among other things — advise the agency with respect to the contents of generally applicable guidance documents (e.g., with respect to preclinical, clinical, and quality data) and with respect to specific product classes. The agency has used outside advisors to flesh out standards for product applications in the past.

PhRMA also urges FDA to follow the same substantive sequence as did the EMA: beginning with general over-arching principles, moving to generally applicable principles by data type, and then concluding with class specific guidance. The EMA began with a general guidance setting forth the basic principles of the biosimilar approval pathway.[22] Next, the EMA created general guidance on quality, preclinical, and clinical issues for biosimilars.[23] The EMA then created class-specific guidance, which address preclinical and clinical issues for product classes such as recombinant erythropoietins, recombinant interferon alpha, and recombinant human insulin. Although the EMA product class choices may be helpful, we assume that FDA would make its own decisions about appropriate product classes for guidance, with the input of U.S. stakeholders.

2. Section 351(k)(8)(E) of the PHS Act permits the agency to indicate in a guidance document that the science and experience, as of the date of the guidance document, with respect to a product or product class (not including any recombinant protein) does not allow approval of a 351(k) application for such a product or product class. What scientific and technical factors should the agency consider in determining if the existing science and experience are sufficient to allow approval for a product or product class under section 351(k) of the PHS Act?

In determining whether the current state of science safely permits approval of a product or class of products under the abbreviated pathway, FDA should 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 can affect clinical outcomes. PhRMA believes that these

[22] EMA Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products (2005).

[23] EMA Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (2006); EMA Committee for Medicinal Products for Human Use, Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (2006).

considerations preclude at this time, among other things, biosimilar vaccines. The benefit/risk ratio is significantly different for vaccines than for other biological products, because vaccines frequently contain live viruses, are generally administered to healthy populations, and are frequently administered to children. Public health considerations counsel against the marketing of vaccines on the basis of abbreviated trials. Other jurisdictions, including the EU and Japan, have taken an extremely cautious approach to including vaccines in an abbreviated pathway.[24] Vaccines are also excluded from the scope of the WHO's guidelines on biosimilar products.[25]

G. 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 for the same period of time, i.e., until the NCE term expires. 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.[26] PhRMA requests

[24] *See, e.g.*, Singapore Health Sciences Authority, Guidance on Registration of Similar Biological Products in Singapore 6 (2009) ("Vaccines, blood or plasma-derived products & their recombinant alternatives, and other types of biological medicinal products, such as gene or cell products used for advanced therapy, and human tissues or cells intended for human application, are of a complex nature and applications for biosimilar products for such products will not be considered at the present moment."); 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); Malaysia Ministry of Health, National Pharmaceutical Control Bureau, Guidance Document and Guidelines for Registration of Biosimilars in Malaysia 3 (2008) ("[T]he biosimilar approach is more difficult to apply to other types of biologics which by their nature are more complex, more difficult to characterise or to those for which little clinical regulatory experience has been gained so far. Therefore, it does not cover complex biologics such as blood-derived products, vaccines, immunologicals and gene and cell therapy products."); 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.").

[25] 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.").

[26] *See* 54 Fed. Reg. 28,872, 28,897 (July 10, 1989) (preamble to 21 C.F.R. § 314.108) (noting that "when exclusivity attaches to an active moiety or to an innovative change in an already approved drug, the submission or effective date of approval of ANDA's and 505(b)(2) applications for a drug with that active moiety or innovative change will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers" and that the alternative approach "would seriously undermine [the value of exclusivity], reducing the incentives for research and innovation in the pharmaceutical industry").

that FDA confirm that it intends to follow the umbrella policy with respect to biological product exclusivity. This would mean, specifically, that: (1) a supplement or subsequent application that was not entitled to its own 12-year period would be protected for any remaining period of exclusivity applicable to the first licensed product to which it is related, and (2) an affiliate or related entity's product that was not entitled to its own 12-year period would be protected for any remaining period of exclusivity applicable to the initial applicant's product. Any other approach would be inconsistent with the agency's longstanding approach to data exclusivity (also referred to as data protection) and, as the agency noted in 1989 when adopting its NCE regulation, would seriously undermine the value of exclusivity and incentives to innovate.

1. In light of the potential transfer of BLAs from one corporate entity to another and the complexities of corporate and business relationships, what factors should the agency consider in determining the types of related entities that may be ineligible for a period of 12-year exclusivity for a subsequent BLA?

The data exclusivity provision of the BPCIA, section 351(k)(7), provides BLAs with 12 years of protection subject to a limitation — in subparagraph (C) — for certain supplements and subsequent applications filed by the same company or a licensor, predecessor in interest, or other related entity. As explained in the prior paragraph, those applications should be protected under the umbrella exclusivity of the first approval. If, however, such an application — for example, a subsequent BLA for the same molecule but for a different indication — is filed by a wholly unrelated company, that application falls within the general rule of section 351(k)(7) and would be protected for its own 12-year period.

FDA asks how to interpret the phrase "other related entity." PhRMA urges FDA to take an approach to this provision that is objective, easy to apply, and consistent with the policy goals of data exclusivity. Specifically, FDA should treat a second applicant as subject to the umbrella exclusivity earned by the first applicant if the two entities are under common ownership and control.[27] This approach would further the objective of subparagraph (C) by ensuring that a separate exclusivity term cannot be claimed by an entity that is ultimately (functionally) the same as one that previously

[27] The common ownership or control test, or other tests that ask essentially the same question, are widespread in the U.S. legal system. For example, in the Medicare context, "related entity" is defined to mean an entity that "is related to the [entity in question] by common ownership or control." 42 C.F.R. § 422.500(b) (Medicare Advantage Program; Contracts with Medicare Advantage organizations; Scope and definitions). In the federal tax context, "related organizations" are defined to mean organizations that stand in a parent/subsidiary relationship or brother/sister relationship or a relationship of financial support. *See* Form 990 Schedule R - Related Organizations: Meaning of Related Organizations (Tip #1) at www.irs.ustreas.gov/charities/article /0,,id+211347,00.html. In the securities law context, "related person" is defined to mean in respect of a company registered under the securities laws a director of such company, any immediate family member of a director or executive officer of such company, or a more-than-five percent security holder of such company or an immediate family member of any such security holder. *See* Securities and Exchange Commission Regulation S-K, Items 403(a) and 404 (Instruction 1).

received exclusivity for the same product. 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.

2. *What factors should the agency consider in determining whether a modification to the structure of the licensed reference biological product results in a change in safety, purity, or potency, such that a subsequent BLA may be eligible for a second 12-year period of marketing exclusivity?*

No products or applications receive "second" periods of marketing exclusivity under the BPCIA. Under section 351(k)(7), if the second biological product is different in safety, purity, or potency from the previously licensed product, it will be entitled to *its own* period of exclusivity, regardless of the sponsor. But the first product's exclusivity will expire as scheduled. Neither product receives more than the statutory twelve years of data exclusivity.

PhRMA recommends that the agency take a straightforward approach to the statutory language in the first licensure provision. Any modification to the structure of the biological product is relevant. Modifications in structure include changes in amino sequence, differences due to post-translational events or infidelity of translation or transcription, and differences in glycosylation patterns or tertiary structure. The statute compels an inquiry into any "change" in safety, purity, or potency, and it does not authorize the agency to superimpose considerations of clinical superiority or benefit. Where the safety profile has changed or the efficacy profile has changed, for example, the statutory standard has been met.

H. Transition Provisions

1. *What scientific factors should FDA consider in defining and applying ''product class'' for purposes of determining which applications for biological products may be submitted under the FD&C Act during the 10-year transition period?*

2. *What scientific factors should FDA consider in determining whether another biological product approved under section 351(a) of the PHS Act could serve as the reference product for an application submitted under section 351(k) of the PHS Act?*

FDA asks two questions with respect to the transition provisions of the BPCIA. PhRMA is responding to both together.

The transition provisions were intended primarily to protect the investments already made by companies considering biosimilar versions of proteins approved under the FDCA. Until March 23, 2020, innovative proteins approved under the FDCA retain their approved new drug applications (NDAs), and biosimilar applications with respect to those proteins may be submitted under the FDCA. PhRMA believes that these biosimilar applications should, from a scientific perspective, be indistinguishable from the biosimilar applications that would have been required under the PHSA, and the standards should reflect that. The applications would need to be filed under section 505(b)(2) as they will need to contain fairly robust preclinical and clinical packages. A subsidiary goal of the transition provisions was to allow innovators of products in the same classes the choice, until 2020, of whether to submit applications under the PHSA or under the FDCA. These applications, PhRMA also believes, will from a scientific perspective be indistinguishable, whether filed as NDAs or BLAs.

PhRMA agrees that FDA will need to identify the "product classes" in question. We believe the agency should first identify the FDCA proteins that will be reclassified under the PHSA in 2020. The agency might look to its 2007 historical overview of protein product regulation for guidance,[28] but we believe that the many marketed insulin and human growth hormone products will constitute the bulk of the list. FDA can then look to EMA product class guidance and the principles that have guided FDA's decisions to promulgate class labeling, in order to place these products into suitable classes.

I. User Fees

1. If the existing fee structure under the Prescription Drug User Fee Act (PDUFA) were to be considered as a model in establishing a user fee structure for applications and supplements for proposed biosimilar and interchangeable biological products, what factors and changes should FDA take into consideration, and why?

Congress amended the Prescription Drug User Fee Act (PDUFA)[29] to include biosimilar applications submitted under section 351(k) in the list of applications subject to application user fees. The current PDUFA fee structure sets fees for two types of applications: (1) applications for which clinical data (other than bioequivalence studies) are required for approval and (2) applications for which clinical data (other than bioequivalence studies) are not required and supplements for which clinical data (other than bioequivalence studies) are required. The fee for the latter set of applications must be half the amount of the fee for the former set. PhRMA believes that biosimilar applications will, for the foreseeable future, contain clinical data. They should therefore be subject to the same user fee as BLAs submitted under section 351(a). This is

[28] Janet Woodcock et al., *The FDA's Assessment of Follow-on Protein Products: A Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY 437 (2007).

[29] FDCA § 736; 21 U.S.C. § 379h.

appropriate; it will ensure that FDA's approval of biosimilars does not overburden the agency and interfere with its approval of innovative new products.

The BPCIA, however, also requires FDA to submit recommendations to Congress with respect to biosimilar user fees after expiry of the current PDUFA authorization at the end of FY 2011. In PhRMA's view, until the agency and industry have experience with actual biosimilar applications, it would be premature to change the fee structure.

2. What factors should FDA take into account when considering whether to recommend that user fees for biosimilar and interchangeable biological products should also be used to monitor safety after approval?

Because biosimilar applications submitted to FDA before the end of FY 2011 are subject to the current PDUFA structure, the agency has the authority to use fees from these applications to address postmarket safety issues.[30] In its recommendations to Congress, FDA should recommend that user fees continue to be available for pharmacovigilance purposes. PhRMA will provide additional comments on the expenditure of biosimilar user fees when FDA publishes its recommendations.

III. Additional Comments

PhRMA offers comments on two issues not raised directly in the agency's *Federal Register* notice: (1) the inherent differences between biosimilar applications and BLAs, and (2) the agency's limited but nonetheless pivotal role with respect to section 351(l) of the PHSA.

First, PhRMA urges 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). As amended, section 351 now describes two mutually exclusive and fundamentally different pathways to market. FDA should 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

[30] 21 U.S.C. §§ 379g, 379h (permitting FDA to expend user fees on "[p]ostmarket safety activities with respect to drugs approved under human drug applications or supplements").

product and thus relies directly or indirectly on the safety and efficacy data in, or FDA approval of, the BLA for the previous product.

PhRMA believes FDA must take a strong position on the distinction between 351(a) and 351(k) applications. 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 some of the proprietary data and FDA findings of safety, purity, and potency relevant to that previously approved product. 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. 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 findings, prior approvals, or previously submitted data. This would give the biosimilar applicant the benefits of an abbreviated pathway without imposing the associated burdens (for example, waiting for the expiration of data exclusivity and confidentially sharing its application with the reference product sponsor for purposes of the patent litigation procedures). 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.[31]

Second, PhRMA believes 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 should therefore require 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

[31] *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).

data exclusivity and a meaningful opportunity to litigate patent infringement issues prior to biosimilar market entry. PhRMA is aware that some have argued the premarket litigation scheme, or at least the triggering step of application disclosure, is somehow optional. There can be no question, however, 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.[32] Further, the balance of the scheme imposes obligations on biosimilar applicants and reference product sponsors that flow directly from the provision in question.[33] Just as it would eviscerate the compromise for applicants to rely on proprietary data in applications they file under section 351(a) without waiting out the data exclusivity term, it would eviscerate the compromise for applicants to rely on proprietary data in section 351(k) applications while ignoring the statutory obligation to provide the information needed for meaningful premarket patent litigation. We believe 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 data exclusivity or the patent litigation scheme. A certification obligation would be simple for FDA to administer, no less ministerial than 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 efforts to solicit the input of stakeholders about implementation of the BPCIA. We hope to continue to serve as a constructive partner, together with other stakeholders, as the agency continues to implement this important legislation.

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

Respectfully submitted,

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[32] *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).

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

Appendix: Regulatory considerations for clinical trial design and statistical studies to support FDA approval of biosimilars.

Introduction:
Less attention has been paid in regulation and guidance globally to general principles and approaches to clinical trial design and statistical studies that regulators could require to support biosimilar approval. In the context of the U.S. regulatory pathway for biosimilars approval authorized under BPCIA, PhRMA urges FDA to consider the following framework when establishing regulation and guidance for the clinical requirements for biosimilar applications. This framework is based and elaborates upon the existing EMA and WHO guidelines for regulatory consideration of biosimilars, as well as appropriate ICH guidances.[1]

Scope:
Based on limitations in precedent and issues of compositional complexity, this document is limited in scope to well-characterized recombinant protein biological products. Other classes of products (e.g., blood products and most vaccine products) are not addressed here.

1.0 CMC Development and Implications for Biosimilar Regulatory Approval--Maintenance of Process Parameters from Early to Late Development

Key Concepts: Changes in process parameters between early and late development, while requiring similar analysis as comparability exercises during reference product development, could have larger regulatory implications during biosimilar development. This is because from a regulatory perspective, an early showing of similarity with a reference product is a prerequisite to the abbreviated regulatory approval pathway, thereby allowing abbreviated non-clinical and accelerated early and late clinical development.

Changes and maturation in manufacturing process parameters are typical during the development of innovator (reference product) biologicals. Often such changes have delayed and/or complicated the development of innovator products, especially when the process changes are significant. The development of an extensive database garnered from experience manufacturing the product allows an innovator to predict whether minor changes in the physical characteristics of its product can be expected to result in changes in the clinical performance of the product.

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[1] EMEA/CHMP/437/04: Guideline on Similar Biological Medicinal Products. 2005. London

World Health Organization (WHO) (2009), *Guidelines on evaluation of similar biotherapeutic products (SBPs)*, Geneva.

EMEA/CHMP/42832/2005: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2005. London

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

For biosimilar products, consideration of these principles may need to be intensified in order to incorporate the different regulatory development concepts that apply to this product class. In the case of biosimilar products, reduced preclinical development, abbreviated early clinical development, and rapid progression to late-phase development may all be enabled by a successful early-stage CMC/quality comparison of the biosimilar product to the reference product. Given the enabling nature of these early comparative data, it may be necessary for biosimilar sponsors to develop a similar manufacturing process to that of the innovator, such as use of the same type of cells for the cell bank. Additionally, changes to the manufacturing process for the biosimilar should be both minimal and minor following the point in time when the successful CMC/quality comparison to the reference product is conducted, upon which the abbreviated regulatory approval pathway is premised.

Analytical methods are generally used in each step to monitor the development and manufacturing processes. Sensitive analytical methods capable of detecting meaningful small differences between the biosimilar and reference innovator products are critical, and these methods should be appropriately validated for statistical process control and assurance. An analytical biosimilarity study should be required to be conducted in a head-to-head fashion. Depending on the type of assays, the study design and statistical analysis may differ. In addition, depending on the variability and quality of the innovator product, the number of representative lots of the innovator and biosimilar product may differ, but the number should provide sufficient statistical power to detect small meaningful differences in terms of the selected quality attributes and endpoints. Due to the inherent nature of biologics (e.g., sensitive to environmental factors such as light and temperature), existing quality guidelines[2], for example, state, "The shelf life of the reference product should be considered when performing a comparability exercise, and its effect on the quality profile should be discussed where appropriate."

2.0 Non-Clinical Study Timing versus the Timing of Clinical Development

Toxicology studies should demonstrate similarity to the reference biological product in order to support regulatory requirements for early and late clinical development.

Consistent with global guidances, only comparative general toxicology studies between the innovator product and the purported biosimilar should be required by FDA to support

[2] EMEA Committee for Medicinal Products for Human Use (CHMP): *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues.* London. 2005.

ICH Q5C: *Quality of biotechnological products: stability testing of biotechnological/biological products.* 1995.

clinical development unless differences are detected[3]. The duration of non-clinical safety studies should either match the duration of clinical treatment, be of the longest duration used by the reference product, or be of sufficient duration to detect differential toxicity between the reference product and biosimilar product, as determined on a case-by-case basis.

For example, if all toxicities detected in chronic toxicology studies are detected in sub-chronic studies, and if severity is similar at shorter time-points, then comparative sub-chronic studies may be sufficient. FDA may consider requiring that doses, regimens, and test species match those used by the reference product in order to support clinical development of biosimilar products.

It should be acceptable to address comparative pharmacology in toxicology species if they are the most relevant species for comparative preclinical pharmacological assessment.

3.0 Early Clinical Development Considerations

3.1 Clinical Development Concepts and Considerations

Key Concepts: Similarity in human pharmacokinetics (PK) and pharmacodynamics (PD) should be tested by the method(s) that are best able to detect meaningful differences; in the case of PD measures, the clinical relevance of these measures should have been established by the reference product or by other means.

The pharmacokinetic concepts that apply to evaluation of innovator products that have undergone significant manufacturing changes and biosimilar products are generally similar. However, it should be recognized that as the biosimilar product does not use the same production process and release assays as the innovator, a greater level of regulatory conservatism will likely be appropriate.

However, the following factors are also generally recognized for all biological products:

- Assays for biological products are often more complex and variable than assays for small molecule drugs. Given this, the automatic application of the standard bioequivalence criteria applied to small molecule drugs will not always be appropriate.

- Further, for biological products with long half-lives, or for which anti-drug antibody formation is likely, cross-over studies may not be appropriate; this will necessarily increase the variability in pharmacokinetic studies.

[3] ICH S6. *PreClinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. 1997.

- Many biological products have their primary activity in tissue spaces other than the vascular compartment, but the vascular compartment is often the only readily sampled compartment. The complex structures of biologics and the complex mechanisms by which they penetrate tissues mean that a showing of PK similarity, in and of itself, may not be sufficient to establish clinical similarity. This is a well-established concept for biological products, and it leads to a greater reliance on pharmacodynamic and clinical measures than is typical for small molecule drugs.

Pharmacodynamic assessments for biosimilars are also generally similar conceptually to those applied to reference product biologics. However, in the case of reference products pharmacodynamic measures are generally chosen based on the ability of the pharmacodynamic measure to predict clinical outcomes. For biosimilars, this same concept should apply, but there should also be focus on the sensitivity of the candidate pharmacodynamic measure(s) to detect *in vivo* differences between the reference and biosimilar products. This is because generally the reference product will have established the clinical relevance (or lack thereof) of the available pharmacodynamic markers. Therefore, sponsors should be requested to carefully consider the discriminatory ability of PD measures when selecting comparative pharmacodynamic measures.

3.2 Statistical Considerations in Early Clinical Development

As mentioned in the WHO Guidelines for Evaluation of Similar Biotherapeutic Products (2009)[4], for regulatory evaluation, the comparative clinical studies should begin with PK and PD studies. Contrary to the situation for small molecule drugs, the traditional cross-over design may not be appropriate for biologics due to their long half-lives and/or likely formation of anti-drug antibodies. As a result, special care should be taken to ensure all relevant prognostic and demographic variables are balanced between the innovator and biosimilar products in the parallel studies in order to reduce the signal to noise ratio. Due to the complex nature of biologics, the choice of endpoints should also be carefully considered. For example, the elimination characteristics such as clearance and/or half-life may be needed in addition to the traditional factors of absorption/bioavailability.

As biologic assays may be highly variable, the standard bioequivalence (0.8, 1.25) boundary for small molecule drugs might not be appropriate for the comparison of a biosimilar and innovator product. Additionally, as described in EMA's biosimilar

[4] World Health Organization (WHO). *Guidelines on evaluation of similar biotherapeutic products (SBPs)*. 2009. Geneva.

guidance (2005)[5], demonstration of bioequivalence is not sufficient for biosimilarity. An approach similar to the reference-scaled bioequivalence (BE) approach discussed for large variability chemical drugs could be considered for PK of biosimilars[6]. In addition to the reference-scaled BE approach, a therapeutic index-scaled BE approach may also be considered[7]. FDA should carefully consider the balance between the risk that a quality product would be rejected with the risk that quality standards would be insufficient to protect patients, and such risks should be pre-defined with consensus from the regulatory authorities on a product-by-product basis.

Because biologics usually have a different pathway for elimination than small molecule drugs, which typically have a common pathway such as the liver, PK and PD may be weakly correlated. Special attention should be made on the selection of clinically related PD parameters, which may be used as a biomarker for the assessment of biosimilarity[8]. The chosen PD parameters are, in most cases, examined in the combined PK/PD studies. Regardless of the study design, the statistical comparison of the innovator and the biosimilar products should be focused on the PD profile comparison.

The criteria (margins) for establishing "biosimilarity" in PK and PD need to be thoroughly considered and clearly justified, likely on a product-by-product basis.

4.0 Late Phase Clinical Development Considerations

4.1 Introduction and Overview

Key Concepts: Similarity in clinical efficacy should generally be demonstrated in the most sensitive population and using the most sensitive endpoints to detect differences, unless this population or endpoints are not clinically relevant and/or not feasible. Extrapolation of these results to other <u>populations within this indication</u> may be feasible,

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[5] EMEA Committee for Medicinal Products for Human Use (CHMP): *Guideline on similar biological medicinal products*. London. 2005.

[6] Haidar, S. H., *et al.* (2007). Bioequivalence approaches for highly viable drugs and drug products. *Pharmaceutical Research*. **25**: 237 - 241.

Haidar, S. H., *et al.* (2008). Evaluation of scaling approach for the bioequivalence of highly variable drugs. *The AAPS Journal*. **10**: 450 - 454.

Liao, J.J.Z. and Heyse, J.C. (2010). "Biosimilarity for Follow-on Biologics". *Statistics in Biopharmaceutical Research*. **In Press.**

[7] Chow, S.C. and Liu, J.P. Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd Edition. Chapman and Hall/CRC Press, Taylor & Francis, New York, New York. 2008.

[8] Chow, S.C., Lu, Q., Tse, S.K., and Chi, E. (2010). Statistical methods for assessment of Biosimilarity using biomarker data. *Journal of Biopharmaceutical Statistics.* **20:** 90-105.

but extrapolation between truly different indications (i.e. indications having a different pathophysiology and/or site of tissue action) may not be possible.

Efficacy assessment is perhaps the area with the most divergence between a reference product biologic and biosimilar products. This is based on the following factors:

- The objective of innovator development is to establish for the FDA that the product has an acceptable benefit/risk balance to support approval, and that the labeling directs appropriate usage. Assurance that the dose and regimen are optimal is also a critical goal. Typically the most clinically meaningful endpoints are considered pivotal, and with few exceptions each indication and population within an indication must be supported by adequate data.

- In contrast, the objective of biosimilar product development is to establish for the FDA that the efficacy of the purported biosimilar is not different in a clinically meaningful way from the reference product. Conceptually, the most efficient manner to achieve this is to conduct a comparative study using the endpoints and population(s) that will most effectively and efficiently establish clinical similarity. Dose and regimen are already established by the reference product and therefore are not variables that need be studied for biosimilars.

- In some cases, it may not be possible to extrapolate data from the most sensitive population to the other populations, and/or enrollment of studies in the most sensitive population will not be feasible. In such cases, alternative clinical strategies could be considered.

- Regarding endpoints, it is noted that the innovator biologic will sometimes have already established that more sensitive (and often secondary) endpoints correlate with the primary (often less sensitive, but usually more clinically meaningful) endpoints. Given this, and given the objective is to demonstrate similarity in clinical activity, the use of endpoints that have greater discriminatory potential could be accepted. In some cases, use of such endpoints will even be necessary to enable biosimilar product development due to the insensitivity of the primary endpoints used during approval of the reference product.

- Extrapolation of data from one *population within an indication* to another population *within that same indication* is different from extrapolation of efficacy data *across truly different indications*, which presents additional difficulties because of the potential implications of differences in pathophysiology, in the site of tissue action between indications, as well as the potential for different patient populations to be on different concurrent therapies that could have clinical affects with the biologic being tested.

4.2 Clinical Development Concepts in Late Development – Consideration of Major Issues

Similar efficacy of the biosimilar and reference biological products will generally need to be demonstrated in adequately powered, randomized and controlled clinical trial(s)[9]. For example, the WHO Guidelines indicate that equivalence designs are preferred for the comparison of safety and efficacy, but acknowledge non-inferiority designs may be considered if justified. In either case equivalence/non-inferiority margins to be pre-defined and justified based on clinical relevance; the selected margin should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within these margins would therefore not be clinically meaningful.

EMA biosimilars guidelines state that in certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification should depend on clinical experience, available literature, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications, and the mechanism of disease. Note that the same molecular mechanism of action is not sufficient to safely extrapolate to indications with different disease processes and target tissues, e.g., Crohns' disease and rheumatoid arthritis; possible safety issues in different subpopulations should also be addressed. The approach should be justified during development and discussed with the FDA.

4.2.1 Choice of Patient Population

For reference biological products, it is common to conduct multiple pivotal studies to obtain data to support regulatory approval for indications in various sub-populations of a given indication (for example, monotherapy, combination therapy, first line versus second line, etc). In some cases, the choice of one of these populations will result in a more sensitive test system in which to detect potential differences in efficacy or immunogenic safety between a reference and biosimilar product. In such cases, the most sensitive population to detect such differences may be the preferred population for study by the biosimilar.

However, when choosing a given patient population for comparative studies with the biosimilar and reference products, one must consider whether that population is considered clinically meaningful, and/ or of enrollment of that population is currently clinically feasible (or if there is a lack of geographic feasibility), and/or if data from that population may be readily extrapolated to other populations.

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[9] We refer to the appropriate WHO and EMA guidelines for additional detail. WHO. *Guidelines on evaluation of similar biotherapeutic products (SBPs).* Geneva. 2009.

EMEA Committee for Medicinal Products for Human Use (CHMP): *Guideline on similar biological medicinal products*. London. 2005.

The first two considerations are addressed in this section; extrapolation between different populations within an indication is discussed below.

4.2.2 Choice of Endpoints

The choice of clinical endpoints for comparative studies between an innovator biologic and a purported biosimilar is a critical consideration, but no blanket criteria will apply to all classes of biologics. Some general statements, however, can be made.

Generally, if the primary endpoint that was used to support the approval of the reference product is sufficiently sensitive to be practical for use in a comparative study, then it should be used as the comparative endpoint.

In some cases, endpoints that served a secondary role in supporting the approval of the reference product are significantly more sensitive than the primary endpoints; in such cases, if supported on a case-by-case basis, the use of such secondary endpoints could be acceptable.

4.2.3 Non-Inferiority Versus Equivalence Designs: Biological and Clinical Considerations

In general, for purposes of establishing biosimilarity, equivalence trials are preferred because they are more sensitive for detecting clinically meaningful differences between lower and upper efficacy margins. In practice, most biological products fall into one of two pharmacodynamic classes, those with a dose response on both sides of the approved dose (or dose range) and those that pharmacodynamically saturate the target at some level and are used at or near the maximal level of clinical effect.

Cytokines generally fall into the former class. For these products, equivalence (two sided test) should be considered by FDA to be the standard clinical trial design, as efficacy greater than the reference product is possible and would be of clinical concern.

In the case of the latter class, the target has generally been completely biologically neutralized at the approved dose. Most oncology antibodies and many anti-cytokine antibodies are in this class. For this class, non-inferiority clinical trial designs may be justifiable because pharmacodynamic activity above the level of the reference biological product is considered highly unlikely from a biological perspective. For such products, a one-sided non-inferiority approach could be acceptable to FDA.

4.3 Statistical Development Concepts in Late Development

After establishing the PK/PD comparability of the innovator and the biosimilar products, a confirmatory equivalence clinical study is needed to demonstrate the biosimilar product is no better and no worse than the innovator product. However, depending on the pharmacodynamic classes discussed in 4.2.4, a non-inferiority study may be acceptable as the study design.

As discussed in recent publications[10], in order to detect a small but meaningful difference between the biosimilar and the innovator products in the efficacy trial, assay sensitivity must be ensured; however, it is very challenging to define the equivalence/non-inferiority margin. The margin has to be pre-specified and justified based on clinical relevance; i.e., the selected margin should represent the largest difference that would not be clinically meaningful[11]. The biosimilar product and the innovator product would be considered biosimilar if the 95% confidence interval of the detected difference is within the pre-specified margin. Information generated from the comparison of innovator product against itself may be useful in determining the margin. Equivalence or lesser variance in the clinical outcome of the biosimilar product as compared to the innovator product may also be assessed in order to enhance the biosimilar claim[12].

Due to the highly complex and heterogeneous nature of biologics, it is critical to understand the variability of the innovator product. Based on the information from the comparative CMC analytical and process study, the appropriate number of representative lots (at least three and preferably more) of the innovator product with different shelf time should be included in the clinical studies in order to properly assess the similarity between the biosimilar and the innovator products.

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[10] Chow, S.C. and Liu, J.P. (2010) Statistical assessment of biosimilar products. *Journal of Biopharmaceutical Statistics*. **20:** 10-30.

Hsieh, T.C., Chow, S.C., Liu, J.P., Hsiao, C.F., and Chi, E. (2010). Statistical test for evaluation of Biosimilarity in variability of follow-on biologics. *Journal of Biopharmaceutical Statistics* **20**: 75-89.

[11] FDA. *Guidance on Non-inferiority trials*. 2010.

ICH E10: *Choice of Control Group and Related Issues in Clinical Trials*. 2000.

[12] Chow, S.C. and Liu, J.P. (2010) Statistical assessment of biosimilar products. *Journal of Biopharmaceutical Statistics*. **20:** 10-30.

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Hsieh, T.C., Chow, S.C., Liu, J.P., Hsiao, C.F., and Chi, E. (2010). Statistical test for evaluation of Biosimilarity in variability of follow-on biologics. *Journal of Biopharmaceutical Statistics* **20**: 75-89.

5.0 EXTRAPOLATION ACROSS INDICATIONS AND INDICATION SUBPOPULATIONS

5.1 Extrapolation Across Populations Within an Indication

As noted above, for reference biological products, it is common to conduct multiple pivotal studies to obtain data and indications in various sub-populations of a given indication (for example, monotherapy, combination therapy, first line versus second line, etc).

5.2 Extrapolation Across Different Indications

The WHO Guideline states that if similarity between the similar and reference biological products has been convincingly demonstrated, the similar biological product may be approved for use in other clinical indications of the reference biological product that have not directly been tested in clinical trials if:

- A sensitive clinical test model used to detect potential differences between the similar and reference biological products has been used.
- The clinically relevant mechanism of action and/or involved receptor are the same.
- Safety and immunogenicity of the biosimilar have been sufficiently characterized.
- If the efficacy trial used a non-inferiority design and demonstrated acceptable safety and efficacy of the similar compared to the reference biological product, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications.
- If efficacy and safety data are to be extrapolated to another approved indication of the reference biological product, care should be taken to ensure that immunogenicity is investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events.

Additionally, the FDA should consider any differences in patient populations between indications that may be relevant in granting indications without clinical data.

6.0 ESTABLISHING SIMILARITY IN CLINICAL SAFETY

With few, or perhaps no, exceptions, safety findings for protein therapeutics are driven by intended/excessive pharmacology or immunogenicity. Given a finding of similar pharmacodynamics and efficacy, as demonstrated through clinical studies concern over the safety of intended/excessive pharmacology should be lessened, and safety databases

similar to those required to support similarity in efficacy should therefore address this concern.

The nature of the data needed to establish adequately similar immunogenicity will vary on a case-by-case basis depending on the protein therapeutic and patient population.

For endogenous proteins with critical biological functions, concerns over immunogenicity will obviously be heightened.

For non-endogenous proteins, concern will generally focus on immunogenicity-related AEs and on immunogenicity that meaningfully alters pharmacodynamics or pharmacokinetics. For proteins with low inherent immunogenicity, it will likely often be infeasible to show rigorous statistical non-inferiority based on anti-drug antibody rates, although assessment of general similarity will be feasible. Very rare AEs potentially related to immunogenicity will generally have to be addressed through post-marketing surveillance.

Methods of immunogenicity assessment will likely need to differ somewhat from biological reference products, as two test articles (the reference product and the similar biological product) are involved in a comparative immunogenicity assessment. FDA should require that this factor be addressed in assay design and development. As the clinical meaningfulness of immunogenicity findings for non-endogenous proteins can be of uncertain relevance in the absence of resulting pharmacokinetic differences, the results of neutralizing antibody assays will be an important consideration.