BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0477, Request for Comments on the Food and Drug Administration Approval Pathway for Biosimilar and Interchangeable Biological Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Agency's Approval Pathway for Biosimilar and Interchangeable Biological Products. BIO submitted initial comments on November 11, 2010, and we were also very appreciative of the opportunity for BIO staff to participate in the Public Meeting held November 2-3, 2010. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are trailblazers in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

In the health arena, BIO member companies have pioneered innovative and lifesaving treatments for patients worldwide using biotechnology processes. These therapeutic and diagnostic products are leading to significant improvements in the care of patients with serious diseases – in many cases providing the first approved treatment for a condition. BIO supported the passage of legislation to enable FDA to approve biosimilars, so that patients living with unmet medical needs will have expanded access to safe and effective medical therapies at lower cost.

Our comments below are grounded by the specific hands-on experience of BIO member companies; experience that is crucial to understanding biological products. These answers are also consistent with BIO's long-standing Principles on biosimilars (http://www.bio.org/healthcare/followonbkg/Principles.asp), which state that any

pathway for the approval of biosimilars must protect patient safety and preserve incentives to innovate. As FDA implements the Biologics Price Competition and Innovation Act of 2009 (BPCIA), we urge FDA to ensure that:

- Patients do not have to accept greater risks or uncertainties in using a biosimilar than an innovator's product. Accordingly, approval of biosimilars must be based on the same rigorous standards of safety, purity, and potency applied by FDA for the approval of innovator biotechnology products.
- Clinical trial evidence and data are fundamental for evaluating and demonstrating the safety and effectiveness of a biosimilar, and must be conducted on a product-by-product basis. In particular, immunogenicity testing is necessary to avoid putting patients at risk of adverse effects from immune reactions.
- Biosimilars must be properly evaluated through post-marketing surveillance and post-marketing clinical studies as needed.
- Biosimilars should be assigned a non-proprietary name readily distinguishable from that of the innovator's version of the product. Assigning the same name to a product that are not the same would be confusing and misleading to patients, physicians, and pharmacists, could result in inadvertent substitution of the products, and would make it difficult to quickly trace and address adverse events that may be attributable to either the innovator or biosimilar product.
- Prescribers are involved in decisions to switch among biological products.
- Biosimilars are not approved until after all statutory protections, including data exclusivity and patent protections, are no longer available for the approved pioneer product. BPCIA implementation should fully respect existing trade secret protections for innovators' data and not permit the use of protected data for the purpose of approving biosimilars. It also must not abrogate or limit constitutional or statutory rights of patent holders to protect against infringement.
- FDA continue to follow a transparent and public process in determining data requirements for the approval of biosimilars by class.
- Workload associated with biosimilars applications does not harm FDA's ability to efficiently review new drugs and biologics, and that new treatments continue to have the highest review priority.

Our specific comments follow.

A. <u>Biosimilarity</u>

A1. 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?

The assessment of a proposed biosimilar product is a side-by-side analytical comparison of the biosimilar against an already-approved reference product. As a first principle, the innovator product and the biosimilar must have the same primary amino acid sequence (except for possible N- or C-terminal post-translational modifications/fraying, if these are known to have no significant impact on efficacy or safety). The amino acid sequence is

the identity of the protein and differences in sequence can impact bioactivity, bioavailability, pharmacokinetics (PK), and immunogenicity. In addition, there should be no evidence of mutation or differential mRNA splicing as detected using peptide maps and other methodologies.

The analytical assessment should be made with both the active protein molecule as well as the formulated drug product. Technical factors to be evaluated besides the primary sequence already mentioned, include chemical/physical properties, higher order structure, post-translational modifications, bioactivity, stability, purity, and product/process related impurities.

The analytical approach should entail utilizing orthogonal methods for many of the attributes described earlier. While current methodology is powerful in many respects, the complexity of most protein pharmaceuticals creates challenges that can only be overcome through employing multiple different modes of investigation. Single measures for any given attribute could be lacking in quantitation, sensitivity, specificity, or scientific content.

Other manufacturing and quality aspects may also need to be assessed in relation to what knowledge lies in the public domain known about the reference product, such as the formulation excipients, equipment, the raw materials used in the manufacturing process for the active ingredient, the container closure system and the cold chain distribution system. A difference in any one of these can potentially have a significant impact upon safety or efficacy of the biosimilar product.

While it is not expected that all process, quality or physico-chemical attributes will be identical between the two products, it must be expected that the quality attributes of the active ingredient and the product will be highly similar and that the biosimilar manufacturer will propose the critical quality attributes and demonstrate the clinical significance of any differences. The results of the comparison at the analytical level forms the basis for determining the extent and nature of non-clinical and clinical testing needed to support marketing approval, in addition to any baseline requirements established by the Agency for a given class of biosimilar.

ICH Q5E "*Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*" may be consulted as the principles described in the guidance apply in concept to a biosimilarity exercise. However, it is important to note that this guidance deals with protein products made by the same manufacturer, and thus the document is not sufficient in and of itself to guide the development of biosimilar products alone. Product comparability testing for intra-manufacturer changes can yield meaningful results because the innovator begins from its intimate and exhaustive knowledge of a process that has proven capable of producing a high quality, safe, and effective finished product over a period of time. Specifically, over the course of time, the innovator accumulates extensive historical data to which the biosimilar manufacturer generally would not have access. The experience of a biological products manufacturer with manufacturing a particular product provides the context within which comparability protocols – as that term is currently used by FDA – can legitimately be used. Absent such context, the impact of any changes to the product or the process by which it is

produced must be assessed differently. It is therefore incorrect to use the term "comparability" to describe the relationship between innovator and biosimilar products, as there is less assurance of continuity in process and testing methods when a different manufacturer is involved.

A2. 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?

Analytics

Analytical methodologies for characterization of therapeutic proteins are increasingly capable of detecting and discerning the nature of structural differences between biologics. This is especially true for the evaluation of primary structures and their post-translational variants which can now be reliably detected, identified, and/or quantified using various techniques. Techniques for evaluation of higher order structures are also improving, although higher order structures present as minor components in a mixture cannot typically be detected or characterized with the same sensitivity as can the characteristics and variants of the primary structures. Some types of product related impurities remain relatively difficult to detect or characterize. These include potentially immunogenic soluble and insoluble aggregates.

Therefore, a comprehensive and robust evaluation of structural similarity presents both an opportunity and a challenge. In comparing a biosimilar product to a reference product it is becoming increasingly likely that certain types of structural differences can be detected, and thus can increase the level of confidence that the similarity of two biologics can be evaluated. However, these capabilities also increase the likelihood that differences will be detected for similar biologics manufactured using two different processes. Many of these differences will not impact the safety or potency of the biologic, but some may. The challenge will be to interpret the relevance of these differences using knowledge about the biologic combined with functional evaluations, non-clinical studies and clinical studies.

ICH Q5E provides some relevant considerations regarding the nature and scope of structural evaluations when comparing two biologics. Specifically, despite the increasing resolving power of certain analytical techniques, it is to be expected that single measures for any given attribute could be lacking in either quantitation or scientific content. Therefore Q5E emphasizes the need to use both routine (lot release) methods and orthogonal characterization methods to evaluate physicochemical properties and impurities as well as functional attributes such as potency and immunochemical properties, if relevant.

The impact of identified or unidentified structural differences should be evaluated in a stepwise manner starting with what is known about the mechanism of action and the development history of the reference product. If there is a possibility that the structural differences could impact potency, immunochemistry, immunogenicity, or PK and the differences are not within the publicly available experience with the reference product,

further studies will be essential to the evaluation of similarity. Even if no structural differences have been detected it will be important to confirm the similarity of the biologic to the reference product using functional assays and appropriate non-clinical and clinical evaluations of the behavior of the biologic.

Biosimilarity should always be evaluated using sensitive *in vitro* and/or *in vivo* functional assays assessing all potential mechanisms of action for the biologic. For monoclonal antibodies this may include immunochemical properties such as Fc receptor binding and antibody dependent cellular cytotoxicity assays in addition to the ligand binding activity. However, such techniques may not be sensitive to all biologically relevant structural differences. For example, parameters that impact the PK of a biologic do not necessarily impact *in vitro* potency. Similarly, *in vitro* methods cannot reliably evaluate the relative immunogenic potential of a biologic. Thus, *in vivo* studies including non-clinical pharmacology (if biologically relevant for an individual product) and clinical evaluations are required.

The scope of such studies is discussed below, but may depend on the findings of the analytical studies, the known limitations of analytical methods, or on other risk factors relating to the product itself and the state of knowledge about its structure and function.

Non-Clinical Studies

Pharmacokinetics

PK characteristics to support the evaluation of biosimilars and reference compounds should be obtained in specifically designed and powered human studies. While non-clinical PK studies may be conducted to facilitate biosimilar development, non-clinical PK studies alone are not an appropriate surrogate for validating biosimilarity. The limited applicability of non-clinical studies may partly result from the unique PK and/or disposition of each compound which can include target mediated disposition and other species-specific challenges.

The animal species in PK studies used should be appropriate and relevant. The choice of species should reflect previous, ongoing or future studies that are used to evaluate the efficacy (pharmacology) and toxicology of these compounds. While it may be that multiple species would meet this expectation, not all need to be examined. In fact, it may often be appropriate to use only one species. The dosage levels, route of administration and dosing regimen should be relevant for those used in the clinical setting. Further, both the reference and biosimilar compounds should generally be included in each study that is conducted.

All PK studies should be properly designed (*e.g.*, number of animals per group, timing of sample collection, *etc.*) to allow the appropriate PK characteristics to be determined. These studies should be designed and conducted in a way that ensures clinical relevance and maximizes the opportunity to detect marked differences between the biosimilar and reference compounds.

Each biologic may have a unique disposition pattern and may require a specifically designed set of studies to define the appropriate PK characteristics. As such, single dose PK studies may often suffice to define the PK characteristics that are most relevant. However, multiple dose PK studies may also be conducted as a component of efficacy/pharmacology and toxicology studies. The design and duration of these studies should be optimized to allow marked differences to be observed between the biosimilar and the reference compounds. Appropriate PD endpoints (*e.g.*, functional assessment or biomarkers) would be valuable to evaluate the compounds. These endpoints should be chosen so as to assure clinical relevance.

If multiple dose PK studies are conducted, then the immunogenicity assessment (*i.e.*, anti-drug antibodies (ADA)) of both the reference and biosimilar should be determined in these same studies. ADA samples should be collected but may not need to be analyzed depending on whether an impact is observed in PK, PD, or if there are potentially ADA related safety findings observed. If needed, ADA sample analysis will allow the study results to be interpreted relative to the timing and type of immunogenicity response to both the biosimilar and reference (*e.g.*, ADA assays may include incidence, presence/absence, timing/transience, selectivity, typing, titer and potential to be neutralizing, where warranted to aid in the interpretation of the study).

Regarding the analytical needs for these studies whenever possible, validated assays should be used for assessing immunogenicity and the quantitation of serum/plasma levels of both biosimilar and reference compounds. Ideally for compound quantitation, the same cross-validated analytical assay should be used for both compounds. For immunogenicity testing, only one assay should be used to compare the biosimilar to the reference product. If non-clinical PK studies would provide support helpful for comparing purification, physiochemical or formulation questions, then they should be conducted according to these same principles.

In summary, non-clinical PK studies will not suffice to designate the similarity of the reference and biosimilar products as this assessment would also need to be conducted using appropriately designed and conducted human trials.

Non-clinical Pharmacology

This section provides only general guidance on non-clinical pharmacological information required for biosimilars. Specific requirements for drug classes may differ, depending on the class; requirements may also differ depending on information gained for bioanalytical comparisons as well as various clinical parameters related to each specific drug product or class, including such elements as therapeutic index, and the type and number of indications for which biosimilar sponsors apply. The demonstration of a high degree of molecular similarity between the biosimilar and reference product should significantly reduce the extent of non-clinical studies because the reference product will likely already have a significant clinical history.

The design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physico-chemical and biological characterization studies should be reviewed from the point of view of potential impact on

efficacy and safety. Non-clinical studies should be conducted with the formulation of the biosimilar intended for clinical use, unless otherwise justified. When developing a biosimilar some existing guidelines may be relevant and should therefore be taken into account; *e.g., Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals* (ICH S6, S6(R1).

As is true for all biologics, biosimilars often require the application of unique approaches to assessing their safety in non-clinical studies. Challenges in the non-clinical evaluation of biosimilars containing biotechnology-derived recombinant proteins are often related to the facts that:

- these products may show species-specific pharmacodynamic (PD) activity such that it is sometimes difficult to identify a relevant species for PD and toxicological evaluation; and/or
- the amount of non-clinical data required to establish preclinical efficacy of a biosimilar product is highly dependent on the product and on substance-class related factors. Factors that often elicit the need for pharmacological assessments include, but are not restricted to:
  - Quality-related factors:
    - Variations in the cell expression system compared with the reference product
    - Presence of a complex mixture of less well characterized product and/or process related impurities
  - Factors related to pharmaco-toxicological properties of the drug substance:
    - Mechanism(s) of drug action are unknown or poorly understood
    - Narrow therapeutic index

Depending on these factors, the spectrum of studies required to establish non-clinical efficacy of the biosimilar may vary considerably and should be designed on a case-by-case basis. For example, in the case of a highly complex drug substance that is difficult to characterize by analytical techniques and which possesses a narrow therapeutic index, the non-clinical development program may encompass a significant portion of the spectrum of studies described in relevant guidelines such as ICH S6. The studies should be comparative in nature and designed to detect marked differences in response between the biosimilar and the reference product, not just the response to the biosimilar alone. Any deviation to this approach should be appropriately justified.

In vitro studies

Assays including receptor-binding studies or cell-based assays (*e.g.*, cell-proliferation or cytotoxicity assays) should normally be undertaken in order to establish similarity of the biological/PD activity of the biosimilar and the reference product. Such data are usually already available from the biological assays described in the quality part of the dossier. Reference to these studies can be made in the non-clinical part of the dossier.

Ongoing consideration should be given to the use of emerging technologies. For example, *in vitro* techniques such as 'real-time' binding assays may prove useful. *In vivo*, the developing genomic/proteomic microarray sciences may, in the future, present opportunities to detect minor changes in biological response to pharmacologically active

substances. If *in vitro* activity does not correspond to the clinical effect it may be necessary to confirm biosimilarity using *in vivo* pharmacology studies to demonstrate similar PD/ pharmacologic activity.

In vivo studies

Non-clinical studies should be designed to maximize the information obtained. Such studies should be comparative in nature (see above), should be performed in (a) species known to be relevant (*i.e.*, a species in which the reference product has been shown to possess PD and/or toxicological activity) and employ state-of-the-art technology. Where the model allows, consideration should be given to monitoring biological/PD activity relevant to the clinical application. These data should usually be available from biological assays described in the quality part of the dossier and reference to these studies can be made in the non-clinical part of the dossier. If feasible, biological activity may be evaluated as part of the non-clinical repeat dose toxicity study (described below). *In vivo* evaluation of biological/ PD activity may not be needed if *in vitro* assays are available, that have been validated to reliably reflect the clinically relevant PD activity of the reference product.

Toxicology

At least one *in vivo* repeat-dose general toxicology study should be conducted, and should follow ICH S6/S6(R1) (ICH S6 should be applied to any biologic therapeutic product). Toxicology studies should be comparative in nature (head-to-head direct comparison to the reference product) and preferably conducted in a pharmacologically relevant laboratory animal species when available. The study(ies) should be designed to detect potential marked differences between the biosimilar and reference product, rather than just to detect effect, and relevant PD and safety endpoints should be incorporated, particularly if there is a known target liability or safety concern with the reference product. The duration of the toxicology study(ies) should be sufficient to detect potential differences between the biosimilar product and reference product. The dose and route of administration should be the same as the reference product. Toxicokinetics should be incorporated in toxicity assessments. Assessment of immunogenicity is discussed below. Other studies, such as safety pharmacology, reproductive toxicity, or carcinogenicity assessments, are generally not needed.

Immunogenicity

In comparative non-clinical studies, an integrated assessment of PK/PD profiles should also include evaluation of immunogenicity potential if any signal of different response to the biosimilar and reference product is observed. Similarly, in a repeat dose toxicity study, ADA response should be evaluated in the context of toxicokinetics (if warranted due to an impact on PK and/or PD or if there are potentially ADA related safety findings observed) to compare differences between the biosimilar to reference biologic. The study duration (dosing frequency and period, and post-dosing period) should be guided by the existing information about immunogenicity potential of the reference product in previously conducted non-clinical studies. If differences in toxicokinetic profiles of the

biosimilar and reference product are detectable, ADA titers (and cross-reactivity with homologous endogenous proteins if applicable) should be determined.

If immunogenicity of the biosimilar is significantly greater than immunogenicity of the reference product in the same animal species (*i.e.*, anti-drug antibody incidence and titers), further characterization of potential differences between two products should be performed.

Clinical Studies

The scope of the clinical program for a biosimilar will depend on multiple factors including the findings and limitations of analytical and non-clinical studies, and the state of public knowledge about the product structure and function. There may be subtle differences between biosimilar products from different manufacturers or when compared to the reference product, which may not become apparent until great experience in their use has been established. Accordingly, a class-by-class approach to biosimilar products is recommended and differences between the biosimilar and the reference product will have to be justified by appropriate studies outlined *a priori* in class-specific guidance (where available). This approach reflects the wide spectrum of molecular complexity among the various products concerned, ranging from relatively simple molecules such as insulin to far more complex monoclonal antibodies. BIO encourages FDA to develop class-specific guidance to address the requirements for demonstrating safety and efficacy of a biosimilar.

Although analytical techniques are increasingly capable of discerning differences between protein structures, there is limited information at present on what degree of differences in structure and function are associated with clinically meaningful effects. Thus clinical testing is needed to demonstrate there are no clinically meaningful differences between the biosimilar and reference products. Depending in part on the molecular complexity and the extent of uncertainty in analytical characterization, the degree of such testing in addition to immunogenicity studies may range from assessments of changes in PD parameters to full blown Phase III comparative trials. The extent of such testing will also be driven by factors beyond the analytics that include the adequacy of characterization of such PD parameters, the requisite size of the safety database and the particular indication in question. Although more limited clinical programs may be possible in certain circumstances, the biosimilar applicant will need to justify the rationale to FDA taking into account these factors.

The clinical program proposed by the sponsor should focus on safety, efficacy and immunogenicity assessments. FDA should follow its longstanding practice of basing feedback and decision-making on scientific, medical, and regulatory considerations appropriate to the sponsor's proposed plan. In addition to appropriate Phase I-III testing (described below), comparative immunogenicity needs to be assessed clinically since the immunogenicity data from reference biologic is considered only supportive. Post-approval pharmacovigilance and risk management is recommended for all biosimilar products based, at a minimum, on the requirements for the reference product.

Initial Assessment of Safety and PK/PD Biosimilarity

The object of the investigation at this stage is to obtain initial safety information and demonstrate biosimilarity of clinical PK or PK/PD to the reference product. It is generally acceptable to start at the recommended clinical dose, unless there are safety concerns or the sponsor is interested in studying additional doses to gain better understanding of the product. A standard *in vivo* bioequivalence study design should be followed where subjects receive a single dose of the biosimilar and reference products on separate occasions with random assignment to the two possible sequences of product administration. For long half-life drugs, crossover studies may not be feasible, necessitating parallel designs. Caution is necessary regarding any extrapolation across patient populations, especially if PK is nonlinear or dependent upon target receptor concentration or receptor uptake. In these cases, PK studies may need to be conducted in different patient populations.

According to the current bioequivalence standard 90% confidence interval for the ratio of the appropriate parameters [AUCs and Cmax] for test and reference products, the acceptance interval should be contained within 80-125%. For highly variable products, the acceptance criteria can be widened when prospectively defined in the protocol and with appropriate scientific justification. It should also be recognized that assays for biological products can be more variable than those for small molecules.

Time-dependent changes in PK can occur upon multiple dosing due to ADA formation . Obtaining PK data following repeat administration in long-term trials in patients should be considered in these circumstances.

Per the EMEA[1]/CHMP "*Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues",* there may be certain cases where comparative PK/PD studies between the biosimilar and the reference products may be sufficient to demonstrate biosimilarity in efficacy. Serious consideration should given to this approach when there is sufficient knowledge of the PD properties of the reference product; at least one robust PD marker is accepted as a surrogate marker for efficacy; and the relationship between dose/exposure to the product and this surrogate marker is well known. If PK/PD studies are used to demonstrate biosimilarity of the biosimilar product to the reference product, caution should be taken to investigate a relevant dose range to demonstrate assay sensitivity as described in ICH topic E10 *Choice of Control Group and Related Issues in Clinical Trials***.** The margins defining clinical biosimilarity of PK and PD parameters must be defined *a priori* and scientifically justified.

Immunogenicity

Immune-mediated responses may be caused by multiple factors, including the drug substance itself, its molecular size, its solubility, and its properties (as well as subtle changes that may affect these properties and which may not detectable by analytical methods), the carriers used in the formulation of the finished drug product, and factors

[1] The EMEA is now referred to as the European Medicines Agency (EMA).

that depend upon the patient. Such immune responses may be mild and benign, or may be severe and even fatal, and there is potential for a biosimilar to exhibit immunogenicity problems that do not occur with the reference product. Therefore, comparative immunogenicity studies should be conducted and should be of sufficient duration to assess the effects of immunogenicity on PK, safety, and efficacy. Some portion of the immunogenicity assessment may need to extend into the post marketing period, for example where clinically meaningful or even serious antibody development has been encountered with the reference biologic or the drug class but is too rare to be observed during pre-market investigation.

The antibody testing strategy including the selection, assessment, and characterization of assays need to be justified, and antibody assays need to be validated for their intended purpose. Possible interference of circulating antigen with the antibody assay(s) should be taken into account. Detected antibodies need to be further characterized and their potential clinical implications regarding safety and efficacy evaluated. Special attention should be paid to the possibility that the immune response affects the endogenous protein's biological functioning.

Efficacy assessment

The primary objective of the clinical study program is biosimilarity, and not generation of new evidence of efficacy. Therefore, wherever appropriate and justified, an abbreviated data package that reduces the number of patients to be enrolled in clinical studies should be considered for biosimilar products though the actual numbers required may be influenced by the need to demonstrate adequate safety of the biosimilar product. A flexible approach may be suitable, using robust, validated surrogate endpoints, if these are available. With regard to patient subpopulations, the most sensitive population toward detection of differences between biosimilar and reference biologic should be considered. Subpopulations with high response rates, which are more homogeneous with regard to disease stage, or those in which validated biomarkers could be used, may be selected for biosimilarity trials. However these subpopulations must be representative of the types of patients and disease presentations likely to be encountered in clinical practice, and consistent with the approved indication(s) for the reference product. As the state of science progresses, new methodologies should be applied wherever possible for biosimilar products to achieve abbreviated clinical data packages and alternate statistical models, *e.g.*, Bayesian statistics can help to optimize clinical trial sample size.

Equivalence or Non-inferiority trials

Designs to demonstrate efficacy of a biosimilar could in concept be either an 'equivalence' trial or a 'non-inferiority' trial. The equivalence trial design must be strongly favored. In an equivalence trial, the primary objective is to demonstrate that the true treatment difference is likely to lie between a lower and an upper equivalence margin that represent clinically acceptable differences. Because the latter situation better represents the statutory standard of no clinically meaningful difference, a comparative clinical trial should be structured as an equivalence trial. For an equivalence trial, both the upper and the lower equivalence margins are needed and the equivalence margin should be pre-specified in the protocol. This margin is the largest difference that can be

scientifically judged as being clinically acceptable. For the purpose of statistical analysis, two-sided confidence intervals should be used and equivalence can be inferred when the entire confidence interval falls within the equivalence margins.

Should applicants believe that there are special circumstances that justify the use of an non-inferiority design, they should be required to provide robust justification to FDA to support this. Such circumstances will be rare. The primary objective of the non-inferiority trial would be to show that the response to the biosimilar product is not likely to be inferior to the reference product by more than a clinically acceptable amount. If a non-inferiority trial design is chosen, the purpose would be to demonstrate that the biosimilar is not worse than the reference product by more than a pre-specified amount. Determination of non-inferiority can be made by testing the null hypothesis that the treatment difference (Biosimilar minus Reference) is equal to the lower equivalence margin.

Whether a non-inferiority or equivalence trial is chosen the boundary or boundaries must be clinically acceptable and chosen prior to the initiation of the study. Appropriate statistical methods should be utilized to ensure that the study is of adequate size to be likely to meet its stated objective.

Use of Surrogate/Biomarker & Clinical Endpoints

Ideally a combination of surrogate/biomarker and clinical endpoints will be available to support approval of the biosimilar. However, in cases where clinical endpoints that measure patient benefit are less sensitive for detecting differences between the reference and the biosimilar, surrogate endpoints may be acceptable if a clear and clinically validated correlation exists to the desired endpoint. The existing regulatory framework (21 CFR 314 Subpart H) allows for accelerated approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity in serious or life-threatening diseases, however this pertains to drugs likely to offer a therapeutic advantage, which is not possible for biosimilars. Thus in order to use a surrogate to demonstrate biosimilarity in a clinical trial there should be strong evidence correlating it with the desired clinical outcome. For anti-cancer agents, long-term survival based on patient benefit endpoints may not be always necessary. It will be appropriate to use surrogate endpoints such as response rate for the purpose of biosimilarity investigation in cases where the reference product may have received accelerated or regular approval based on the same endpoint in an area of unmet medical need.

In cases where surrogate endpoints are not available and clinical outcomes data are needed, biomarker data can supplement those data, potentially decreasing the amount of clinical outcomes data needed and increasing confidence in the clinical similarity of the biosimilar and reference products.

Use of biomarkers or surrogate endpoints may be appropriate to support approval of either all the indications for a biosimilar product that may have multiple indications and/or to support additional indications after an initial indication has been investigated using established clinical endpoints. However there must be strong evidence that the biomarker is predictive across indications to permit its use in any type of extrapolation.

Only clinically robust, validated biomarkers that were used to obtain the initial approval of the reference product or those that have since been clinically validated are appropriate. Addition of biomarkers on top of clinically validated outcome measures can serve to provide additional reassurance that the biosimilar product is similar to the reference product.

Safety assessment

Because of the specificity of therapeutic biologics, off-target effects are generally not anticipated and the majority of adverse events are likely to be mechanism-based. Given this, a thorough comparative assessment of PD may support similar mechanism-based safety. Off-target effects should be evaluated on a case by case basis and the biosimilar applicant will need to account for differences that do exist. Thus, demonstration of comparable pharmacological activity, exposure and potency of the biosimilar to the innovator in pre-clinical studies, Phase I, and in the efficacy safety and immunogenicity evaluation in Phase III provides data to supplement the evaluation of mechanism-based safety. Safety data should be collected in long term extension trials as well as post marketing studies in order to have a large enough sample size to detect rare events that may occur with long term exposure or in populations not studied in clinical trials. A robust risk management program should be implemented for the biosimilar product to collect safety data on the biosimilar product to assess safety, and immunogenicity in the post-approval patient population.

Safety risk profiles may differ between indications because of variables such as concurrent conditions or concomitant medications so extrapolation of safety data to other indications will often be inappropriate. In some cases, biosimilarity of safety could be demonstrated in an indication that has high sensitivity toward detection of differences and extrapolated to all other indications.

A3. 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?

Each product must be considered on a case by case basis as to what range of "structural differences" is acceptable. The range will vary by where these structural differences occur in the protein, what is known about the impact on safety and efficacy of these differences, and the patient population in which the drug is expected to be used. Any structural difference that would impact the amount of drug administered would be unacceptable as this implies a change in PK or *in vivo* bioactivity.

Differences in primary sequence should automatically remove the biosimilar from consideration as a biosimilar (except for possible N- or C-terminal post-translational modifications/fraying if these are known to have no significant impact on efficacy or safety). The amino acid sequence is the identity of the protein and differences in sequence can impact bioactivity, bioavailability and immunogenicity.

Minor differences in post-translational processing may be justified in some circumstances, but the secondary and tertiary structures should remain highly similar to those of the reference product. Techniques for evaluation of higher order structure can be relatively insensitive to minor differences in structure, so a lack of similarity in such attributes could indicate a significant deviation in structure that could impact safety, efficacy or immunogenicity. Furthermore, any differences in processing should not affect the bioactivity or binding affinity of the biosimilar as these could impact the product's PK and PD.

In some cases deviations in post-translational processing affecting the proportions of charge variants or glycoforms may be acceptable. If critical quality attributes are known, and if the differences in product variants that are observed are in attributes unrelated to safety and efficacy, then it is possible to justify a variant profile outside of the historical range of the reference product.

A4. 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?

We foresee no circumstances in which an applicant of a 351(k) application would not submit non-clinical studies and clinical studies. Non-clinical PK and/or toxicity studies are always necessary, and should be comparative unless no pharmacologically relevant species is available. Nonclinical testing is the standard for minimizing risk to patients prior to exposure to investigational biologics. Therefore, if no pharmacologically relevant species is available, the biosimilar applicant must still demonstrate that it can manage the risks of taking the investigational product into humans.

While the ability to characterize protein products has improved over the last decade (particularly for proteins of smaller size with no post translational modifications), there are more factors to consider than just analytical characterization. Safety issues have arisen with the use of protein products where no differences were detectable through analytical characterization (*e.g.*, protein interactions with primary container closure materials). In addition, non-clinical studies, by themselves, should not be used to determine biosimilarity *in lieu* of appropriately designed and conducted human studies, because of the inability of non-clinical data to predict human PK and immunogenicity.

Human studies should always be done to assess the PK of a biosimilar and reference compounds. These studies must be well-designed and robust to allow the appropriate PK characteristics and PD effect to be determined. Non-clinical PK studies alone are not a surrogate for validating biosimilarity, which may partly result from the unique PK and/or disposition of each compound.

Clinical and non-clinical studies are necessary to evaluate toxicities that cannot be detected through analytical studies.

B. Interchangeability

B1. 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?"

Many factors should be taken into account when a designation of interchangeability is to be considered, including the complexity of the product's structure and formulation, degree of structural similarity between the reference molecule and the biosimilar, mechanism of action, therapeutic index, safety and immunogenicity profile of the innovator molecule, post-marketing efficacy and safety data with the biosimilar product proposed to be interchangeable, overall risk benefit profile, intended therapeutic area, route of administration, and whether the use would be for acute versus chronic treatment, and therapeutic index. Patient factors such as age, gender, ethnicity, disease state, stage of disease, comorbidities, and concomitant medications should also be considered, to provide assurance of safety in all relevant subpopulations.

The provisions of BPCIA make clear that the approval criteria for biosimilarity are substantively and legally different than the standards for establishing interchangeability. The statute sets forth two distinct additional requirements for interchangeability. The minimum mandatory requirement for any biosimilar product to also be deemed to be interchangeable is that the product must "**be expected to produce the same clinical result** as the reference product **in any given patient**."[2] Both single-use and repeat-use products must satisfy this requirement, but in addition, repeat-use product sponsors must also demonstrate that the "risk in terms of safety or diminished efficacy of alternating or switching between use of the [biosimilar] biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." This results in a higher standard for similarity in clinical trials, separate from and in addition to the need for switching data. Because the statute explicitly states that biosimilarity is a prerequisite, Congress clearly intended that FDA require additional data in order to support a finding of interchangeability. Necessarily, the statute contemplates a two-step process, with biosimilarity the only approval that is likely to be achieved upon first marketing approval, absent compelling data.

A stringent understanding of "expected to produce the same clinical result as the reference product in any given patient" is vital when products will be used interchangeably in patients. Practically speaking, there may be little to no way to track the specific product administered to a particular patient, when substitution is in play. In developing a regulatory standard for meeting the "same clinical result in any given patient" standard, FDA should focus on the need to rule out any reasonable potential for a different result in any individual patient. This should involve evaluating individual patient outlier results – rather than simply average clinical results – in clinical trials and other research, as well as careful assessment of the post-marketing experience with the biosimilar product. Individual level information – rather than just population level information from clinical trials – will be required. Clinical trials provide information on the "average effect" and report on population response. Given the greater potential for an

[2] 42 U.S.C.§ 262(k)(4)(A)(ii) (emphasis added).

individualized response to a biologic product, evaluation of the more individualized patient response is necessary. This information should be collected from post-marketing data sources including patient registries, open-label studies, and pharmacovigilance surveillance and analysis. Careful assessment of individual patient response differences, such as needed dosage adjustments, and adverse events will be crucial with special emphasis on antibody development and immunogenic responses.

Given the strictness of the legal standard that applies to interchangeability, "the same clinical result…in any given patient," clinical data must be provided for each labeled indication. Extrapolation of indications may be acceptable for determination of biosimilarity (if the mechanism of action is very well understood and is the same for those indications). However, to be deemed an interchangeable biosimilar the 'same' efficacy and safety should be shown in clinical trials in each of the indications included in the reference product labeling. It may not be necessary, however, to have a chronic switching study for each indication.

There should be a randomized (and ideally blinded) comparator study for each indication and the duration of exposure for chronic therapies must be justified by the sponsor. Guidance will be needed for each product type to establish acceptable confidence intervals for analysis. The study endpoint for biosimilar interchangeable approval should be the same endpoint as that in the innovator's registration study (or the current standard).

Standard clinical methodology (*e.g.* parallel equivalence or non-inferiority trials) cannot establish clinical "sameness" in a population unless highly sensitive endpoints are available. Given this, demonstrating that a drug meets the legal standards for interchangeability may not be feasible in some cases.

B2. 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?

The goal is to demonstrate that switching back and forth between the biosimilar and the innovator reference product does not produce an immunogenic response, unexpected safety issues, or differences in effectiveness in individual patients. Ultimately, it is imperative that prescribers are assured that individual patients can switch back and forth between the biosimilar and the reference product without an impact on efficacy or safety.

Clinical trials provide information on the "average effect" and report on population response. Given the greater potential for an individualized response to a biologic product, evaluation of the more individualized patient response is necessary. This may take the form of patient registries, open-label studies, and a rigorous post-marketing surveillance plan post-approval as a biosimilar, absent compelling data. The post-marketing surveillance plan should be able to distinguish between treatment emergent safety signals (immunogenicity, loss of efficacy, heightened response, *etc.*) that were due to the biosimilar, switching from the reference product to the biosimilar, or switching back to the reference product.

Crossover studies with multiple switches over an appropriate period of time (switching schedule/design based on the PK/PD of the products) to evaluate the impact on safety and efficacy to the patient should be carefully considered while balancing the need for safety and efficacy data. The clinical trial design should take into account the overall length of expected therapy and that therapy with an innovator or a biosimilar could occur for a year or longer before a switch is made, if the therapy is a chronic treatment.

Furthermore, there must be assurance that patients would not be deprived of therapeutic options as a result of switching (*i.e.*, patients would develop a reaction in a switch to a biosimilar which would render use of the reference product ineffective or unsafe). The program for the proposed interchangeable biosimilar product would have to offer assurance that the consequences of switching products in individual patients would not render the reference drug less effective or cause safety issues, in each of the approved indications.

C. Patient Safety and Pharmacovigilance

C1. 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?

Pharmacovigilance activities must be guided by the fact that biologics:

- are complex and challenging to characterize
- are affected by manufacturing, formulation, SKU, primary container closure, and delivery system characteristics
- can produce a highly individualized response in patients associated with, or independent of, protein structural and other product characteristics
- product properties can result in unique immunogenic responses in patients
- reference products and biosimilars are similar, not identical
- a carefully designed pharmacovigilance effort is necessary for a product to graduate from being a biosimilar to being interchangeable, including the application of each of the above principles to multiple potential indications

C2. What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?

Pharmacovigilance standards should be equally rigorous for reference, biosimilar, and interchangeable biosimilars. Specific requirements may vary based on what is known about the reference product and product class at the time of approval of the biosimilar and/or interchangeable biosimilar.

Robust post-marketing data collection and evaluation are essential to assure product safety and effectiveness - especially because some serious rare adverse events will not be seen in a clinical trials. Although pre-market studies cannot be expected to detect rare adverse events, there should be careful consideration of the size and scope of the pre-

approval program based upon the profile of the innovator product and the disease in question to permit the pharmacovigilance program to be oriented towards areas of potential risk. Pharmacovigilance programs should be able to distinguish between adverse events associated with reference, biosimilar, and interchangeable biosimilars. Because the standard of interchangeability is more rigorous than that of biosimilarity additional attention to the pre-approval program may be necessary.

Identification of the exact product received by the patient is essential to recognizing safety issues quickly and limiting risk to patients. Therefore a unique brand and nonproprietary name are essential. Biosimilars are "similar" but not "identical" to the reference product, and their safety and effectiveness profiles may differ from that of the reference product. Assignment of the same nonproprietary name to a biological medicine and any biosimilar versions may be taken to imply that these products are pharmacologically interchangeable when they are not. BIO takes the position that in order to accommodate the subsequent advent of new biosimilars each biological medicine should have a distinct INN to permit tracing an event to the product administered.

Differing safety profiles of reference and biosimilar product could be due either to intrinsic differences between products or lot-to-lot variation in product quality attributes for the biosimilar. Lot numbers of the product administered are always provided by the manufacturer, but experience has shown that they are not always reported by the end user communicating an adverse event. Efforts should be made to make sure that lot numbers are collected. This is general good practice to differentiate not only a biosimilar from the reference product, but one lot of a drug from other lots when made by the same manufacturer.

C3. Assuming each product is 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?

A standardized naming system for the nonproprietary name with distinguishing prefix and suffix should be considered. While a distinct INN could consist of the same stem name as the innovator plus a unique suffix (such as "-alpha" or "-beta" or the manufacturer's name), distinguishing also by prefix provides more apparent traceability. Due to the potential for incorrect naming based only on non-proprietary name, both proprietary and non-proprietary names should be collected on adverse experience reports.

C4. What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent inadvertent substitution of products not identified as interchangeable without the intervention of the prescribing health care provider?

BIO believes that prescribers and patients should be provided with specific information regarding each biological medicine in order to make an informed decision regarding the

use of the product. Therefore, we believe it is essential that each biological medicine, and each biosimilar version of it, have its own individual or "original" labeling (the United States prescribing information (USPI) and patient labeling). The labeling should provide information for physicians and patients on the status of the biologic (*i.e.*, has it been deemed to be a biosimilar or an interchangeable biosimilar by FDA) stated in clear language that can be easily located on the label. Product labeling should include a prominently-displayed standard warning against switching products without the involvement of the prescriber if the product is not deemed interchangeable. The USPI must reflect the data package on which the biosimilar was approved, which includes the nature of the clinical studies. This will also provide information to a prescriber as to whether a product was approved as a full biologic licence application (BLA) or as a biosimilar. Unless restricted (see below), inclusion of data from studies of the reference product should also be considered.

C5. 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?

The agency may wish to consider whether a database/reference system should be available to help healthcare providers determine the product status (biosimilar/interchangeable) at the site and time of prescribing or dispensing.

D. <u>The Use of Supportive Data and Information</u>

D1. 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?

From a legal perspective BPCIA authorizes reference to a single U.S.-licensed biologic product; formal reference to products that are not licensed by FDA are not permitted. Thus, in brief, the statute dictates the biosimilar product be evaluated against only one reference product, which itself must be a single biological product licensed under section 351(a), and that all data (analytical, nonclinical, and clinical if required) relevant to section 351(k) be compared in a scientifically valid manner, to an FDA-approved reference product.

From a scientific perspective, even if permitted by BPCIA for use as supportive data, introducing a third comparator product (in addition to the biosimilar and reference product) would raise additional scientific questions. In this case, it is imperative that a highly cautious approach be taken when accepting data from comparative studies using non-U.S. product since such products may differ significantly from the U.S.-licensed product. For example, there may be differences in the structure or purity of the product. There may also be differences in manufacturing or raw materials, formulation, filling, packaging, processing or handling. Additionally, the manufacturing and quality control standards could be different, and versions of the non-U.S.-approved product may be

physically different (*e.g.*, different packaging or presentations) all of which could have clinical implications for the patients receiving the product.

Comparative trials involving foreign products made by companies that do not also hold the U.S. license should not be accepted by FDA. It would be very unlikely that such products would be manufactured using the same procedures, materials and quality controls and hence the concerns raised above about potential differences could not be addressed.

Even if the non-US comparator product is manufactured by the same company holding the U.S. 351(a) license, the biosimilar applicant must establish a scientific basis for using this comparator product for supportive data. Without knowledge of the manufacturing processes for the US reference product and the foreign comparator product, it may be difficult for a biosimilar sponsor to thoroughly analyze the differences between the products. It is therefore suggested that FDA require at least the following showings with respect to drug substance and drug product (where applicable) when determining whether to accept supportive data from a non-US comparator product:

- The foreign comparator product and the FDA-approved reference product were manufactured in facilities licensed and inspected by the ICH regions (U.S., Europe, Australia, Canada, or Japan) in accordance with current good manufacturing practices.
- Preferably, the drug substance for reference and comparator products should be manufactured in the same U.S.-licensed facilities (as shown by available information).
- Analytical data, and if necessary bioequivalence data, show that the foreign comparator product and U.S. reference product are highly similar.
- The foreign comparator product has the same formulation, and primary packaging as the U.S. reference product.
- The foreign comparator product is approved and has been widely marketed for an appropriate length of time in a region that has a regulatory authority comparable in sophistication and expectations to FDA, as well as a pharmacovigilance system at least as robust as those in the United States.

E. Definition of a Biological Product

E1. What scientific and technical factors should FDA consider in developing a regulatory definition for the category of "protein" (as distinguished from peptide or polypeptide)?

All proteins are polypeptides, but not all polypeptides are proteins. The definition as to when a polypeptide becomes a protein has been somewhat arbitrary over the years. By and large, one commonly accepted distinction as to when a polypeptide should be considered a protein is when a polypeptide has stable higher order structure that is integral to its function. Consequently the scientific and technical factors that FDA should

consider relates to the assessment of a stable conformational state with higher order structure which when absent renders the product inactive.

E2. What scientific and technical factors should FDA consider in developing a regulatory definition for the category of "any chemically synthesized polypeptide"?

Utilizing the distinction cited in the previous question, the regulatory definition might focus on chemically synthesized polypeptides that do not have stable higher order structure with stable biologic activity. This would then allow chemically synthesized proteins, which would by definition have stable higher order structure that is required for activity, to be regulated as biologics.

F. Guidance

F2. 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?

To ensure that manufacturers provide the detailed data content and application information necessary to meet statutory requirements for marketing approval of a biosimilar or interchangeable product, BIO strongly recommends that FDA issue timely guidance outlining the Agency's general framework and criteria for implementation of BPCIA. The guidance-development process should be conducted prior to FDA approval of any biosimilar product. Issuance of guidance prior to product approval will allow FDA to leverage stakeholder feedback on the appropriate data requirements for biosimilars, while avoiding premature approval of specific biosimilar applications that may or may not meet the data requirements ultimately established.

After issuance of a general framework guidance, BIO recommends that FDA issue guidance specific to product classes. Because of the molecular complexity among different biologics, such guidance will establish the specific data requirements required to show biosimilarity and/or interchangeability for each class of biological products.

Where there is limited scientific knowledge and FDA has limited regulatory experience with respect to a class of biological products, as is currently the case, for example, with cellular and gene therapies, FDA should defer consideration of a biosimilar pathway for such product class until such future time where robust product specific data requirements can be established.

Although BPCIA does not require FDA to issue guidance prior to the review and approval of biosimilar applications, the guidance development process provides an opportunity for public input and generates several important benefits. Guidance development provides transparency in the Agency's decision-making, thereby

establishing consistency, a level playing field, and enhancing public confidence in the safety of biosimilar products. Availability of guidance will also afford industry a degree of regulatory predictability and therefore, encourage the entrance of more biosimilar manufacturers to the market. The opportunity for public input will allow innovators to contribute knowledge gained from lengthy experience in biologics manufacturing to the BPCIA implementation process. Through public comment, healthcare providers, academic institutions, and patients can also provide valuable insights and data on reference products that may be relevant to the approval of biosimilar products.

Therefore, BIO supports the approach taken by the European Medicines Agency (EMA) in developing guidelines outlining the basic principles the health authority would apply to its review of marketing applications for biosimilars. For example, EMA pursued a science-based, transparent and open process, and conducted public scientific workshops soliciting stakeholder input. Initially, it established basic principles for all biosimilars and then drafted and sought public comment on concept papers and broad guidelines addressing product quality and nonclinical/clinical issues. These general guidelines were followed by specific guidelines with testing recommendations for product classes.

On average, the European Union has completed biosimilar product-class-specific guidance in approximately 12-18 months. As FDA conducts its own guidance development, the Agency can reap the benefits of what has been and can be learned from the EMA experience and leverage this knowledge into the timely development and issuance of guidance on biosimilars.

G. Exclusivity

Clarifications

As an initial matter, BIO believes it is important for FDA to make two clarifications regarding the proper interpretation of the statute's exclusivity-related provisions.

First, as referenced in the FDA notice, BPCIA defines a set of circumstances under which a supplement or subsequent BLA filed by the same sponsor or manufacturer of a reference product is ineligible for its own "date of first licensure" for purposes of applying the statute's exclusivity provisions. It is important, however, that this language not be mistakenly interpreted to imply that such subsequent approvals are ineligible for any period of exclusivity. Such a reading would be inconsistent with FDA's longstanding interpretation of the new chemical entity exclusivity (NCE) provisions under the Hatch-Waxman amendments to the Federal Food, Drug and Cosmetic Act (FFDCA). Under that policy, subsequent applications containing a previously approved NCE are protected for the remaining period of exclusivity applicable to the original product.[3]

A contrary reading also would be inconsistent with the intent of this section of BPCIA, which was to maintain incentives for development of next generation products and

[3] *See* 54 Fed. Reg. 28,872, 28,897 (July 10, 1989).

product improvements while avoiding the grant of a separate 12-year exclusivity period for products with certain types of changes to existing products.

BPCIA accomplishes this balancing of interests by ensuring that any subsequent BLA that is structurally different from an existing product in a way that affects product safety, purity, or potency is treated as a new product, with a separate 12-year period of exclusivity. There are, however, less extensive but nonetheless worthwhile changes – such as new indications, strengths, or dosage forms that do not involve a change in molecular structure – which sponsors of already-licensed products should also be encouraged to pursue. A complete lack of exclusivity in this context would eliminate incentives for manufacturers to make beneficial changes to their existing products, as those improved products would be immediately subject to biosimilar competition while the original product might still have some remaining years of exclusivity. It is important for a sponsor to know that products with such changes, although not granted a separate exclusivity period, will receive the protection of any remaining portion of the existing 12-year period that was granted to the initial product.

Accordingly, the proper interpretation of this provision is that a subsequent BLA or supplement that falls within the statutory criteria in subsection (k)(7)(C) is protected by the remaining period of exclusivity that applies to the "first licensed" BLA. Thus, BIO believes that it is important for FDA to clarify that BLA supplements and full BLAs that may not themselves be eligible for 12 years of exclusivity because they seek certain non-qualifying changes to already-approved products will nevertheless benefit from any remaining exclusivity for the underlying, previously-approved biologic.

Second, the notice states that, in certain circumstances, "a subsequent BLA may be eligible for a second 12-year period"[4] of exclusivity. This is inaccurate in that the statutory language ensures that no product can obtain a "second" 12-year period of exclusivity. The same sponsor or manufacturer of a reference biological product can obtain a separate 12-year period of exclusivity for a subsequent BLA that makes a structural modification to the existing product that affects safety, purity, or potency. However, in such cases the exclusivity period attaching to the previously-licensed reference product is not extended in any way. Rather, there is a new product, different from any previously-licensed product, that obtains its own 12-year period of exclusivity.

G1. 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?

FDA's question refers to section 351(k)(7)(C)(ii), which provides that exclusivity for a subsequently-filed BLA related to a previously-licensed product may not be eligible for its own 12-year period of exclusivity if the subsequent application is filed by either (a) "the same sponsor or manufacturer" of a reference product; or (b) "a licensor, predecessor in interest, or other related entity."

[4] 75 Fed. Reg. 61500 (October 5, 2010).

As the FDA notice indicates, the meaning of the term "other related entity" is not defined in the statute. BIO believes that, consistent with common canons of statutory interpretation, this term should be read in the context of the terms that surround it – "licensor" and "predecessor in interest." In this regard, we note that current FDA regulations define "predecessor in interest," in the context of acquiring or transferring new drug exclusivity as *"an entity, e.g., a corporation, that the applicant has taken over, merged with, or purchased, or from which the applicant has purchased all rights to the drug.*"[5] In the preamble to this regulation, FDA stated that "predecessor in interest" in this context includes "licensors, assignors, joint venture partners, or other parties" who have granted to the applicant exclusive rights to a new drug application or data upon which exclusivity is based.[6] To be consistent with the Agency's prior interpretation of similar terms, BIO believes that, in the context of the biosimilars statute, the phrase "licensor, predecessor in interest, or other related entity" should be read as a whole to mean a subsequent BLA applicant that previously had granted exclusive rights to the reference product to the holder of the reference product BLA.

G2. 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?

As discussed earlier, a subsequent BLA filed by the same manufacturer (or related entity) of a reference product can obtain its own 12-year period of exclusivity if there is a modification to the structure of the reference product that results in a change in safety, purity or potency. This is an extremely important provision in that it assures that a manufacturer of an approved biologic will be incentivized to develop a second-generation biologic of benefit to patients.

This statutory provision clearly indicates that any modification to the structure of a reference biologic that results in a subsequent product with safety, purity or potency differences from the reference product qualifies for its own 12-year period of exclusivity. Examples of the type of changes that BIO believes would qualify as modifications to the structure of a biologic for purposes of this section include a modification of the primary amino acid sequence of the active ingredient; a modification of critical post-translational features of the active ingredient; changes in the components of the biological product; as well as any other changes to the structure of the product. These are only examples of changes that would result in a structurally modified subsequent product; BIO believes that it would be impossible to predict or describe the nature of all such changes, as science and product development are constantly advancing. BIO believes it is important that FDA recognize this evolving nature and not prescribe or limit the types of changes or modifications that would qualify as "structural" and therefore, if they result in a change in safety, purity, or potency, qualify the subsequent product for its own 12-year period of exclusivity. In accordance with the plain language of the statute, FDA should make clear in its implementation of this provision that the factor that limits the applicability of the 12-year exclusivity period is the consequence of such a structural change – whether it

[5] 21 CFR § 314.50(j)(iii).
[6] 59 Fed. Reg. 50338, 50358 (October 3, 1994).

results in a change in safety, purity, or potency – but not the nature or extent of any structural change itself.

H. Transition Provisions

H1. 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?

BIO recommends that FDA define the term "product class" broadly and provide industry and the public with a list of proposed product classes. At a minimum, BIO assumes that product classes will include insulins, growth hormones, menotropins, hyaluronidases, naturally sourced antibodies, and enzyme products such as urokinase, algucerase, and imiglucerase, and pancrealipase. In addition, scientific factors such as complexity of the molecule, recombinant or non-recombinant origin, existence of reliable biomarkers, indication and safety profiles of each class should be considered. Product classes should be sufficiently well-described so that it is possible for manufacturers to determine easily whether products fall into a particular class.

In addition, consistent with its general efforts to harmonize international product standards and practices, FDA should consider adopting the relevant standards, recommendations and product classes used by the EMA in connection with its review and approval of biosimilars, among others, growth hormones and insulins. Use of existing EMA classes and standards that have been market-tested would enable FDA to provide a prompt and reliable basis to move forward with transition of these products, with assurance that the standards will effectively protect patient health.

Additional Relevant Questions for Transition Products

In addition to the above questions concerning transition products, there are a number of issues that FDA will need to consider as it begins to implement the provisions of BPCIA. These questions include issues relating to transition of Orange Book rating system under 505 to 351 (BIO believes there should be no transfer of the ratings); the application of the exclusivity provisions of BPCIA to transition products (BIO believes that the products should be fully eligible for BPCIA exclusivity); and data requirements for determining interchangeability of transition and their potential biosimilar versions (BIO believes that there should be an indisputable demonstration through clinical trials of clinical equivalence and absence of clinical effect in the event of switching between products for an interchangeability determination).

I. Biosimilar User Fee Questions

I1. 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?

BIO recognizes that applications for approval of biosimilar products will raise novel and complex questions of science and law, requiring substantial time and additional resources to ensure a thorough regulatory review for safety, purity, and potency. In order to avoid slowing down FDA's review and approval of new therapies and cures, many for currently untreatable and serious diseases, FDA must ensure that workload associated with biosimilar applications does not harm the Agency's ability to efficiently review new drugs and biologics, and that new treatments continue to have the highest review priority.

To provide FDA with dedicated resources for biosimilar review, Congress expressed support for the development of a biosimilar user fee structure to be enacted by October 1, 2012. As transitional measures, Congress authorized FDA to collect PDUFA user fees with biosimilar submissions and instructed the Agency to collect and evaluate the costs of reviewing biosimilar applications by October 1, 2010. Congress also directed FDA to "develop recommendations to present to Congress with respect to the goals, and plans for meeting the goals, for the process for the review of biosimilar biological product applications submitted under section 351(k) of the Public Health Service Act (as added by this Act) for the first 5 fiscal years after fiscal year 2012." These user fee rates and performance goals should be determined "after negotiations with regulated industry" and based on consultation with Congress, scientific and academic experts, healthcare professionals, patients and consumer groups, and industry.

When establishing the biosimilars user fee program, there are a number of advantages to drawing upon established precedents under the current FDA user fee programs. For example, user fees provide FDA with consistent, multi-year funding that allows both the Agency and industry to conduct long-term budgeting and planning. Additional user fee resources allow the Agency to conduct expeditious review of an application while continuing to employ the highest standards of empirically based product evaluation. As a "fee-for-service", user fees also provide sponsors with predictability that the Agency will manage reviews towards pre-determined performance goals that do not pre-suppose the outcome of the review.

A biosimilars user fee structure should incorporate the following elements from existing user fee programs:

- Transparent fee rates published in the federal register grounded by reasonable cost estimates of FDA's resource needs and workload.
- Annual fee adjustments for inflation and workload.
- Predetermined definitions and triggers to ensure that fees are spent on biosimilar applications and are not redirected to unrelated FDA or government activities.
- Conversely, firewalls should be implemented to ensure that user fees, appropriations, and FTEs from other FDA programs, such as new drug and biologics review, are not diverted to biosimilar review in the event of a funding shortfall.
- Transparent review management processes and publically reported metrics and annual reports to track program performance and finances.
- Sunset of the program at specified intervals to provide an opportunity to make course corrections and other related improvements.

I2. 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?

Careful post-market monitoring of the safety of a biologic, whether innovative or biosimilar, is extremely important and should be funded by user fees. Both FDA and the innovator industry have embraced a "life-cycle" approach to product evaluation. In the words of Commissioner Hamburg, "we are in the beginning of a new era for drug safety where protecting public health means that FDA's responsibility doesn't end when we grant a product market approval; that is merely the first check point in ensuring safety."[7] Under PDUFA IV, innovator user fees were extended to support this type of post-market safety evaluation by FDA.

Biosimilar user fees should also support a lifecycle approach to product evaluation. Patients should not have to accept greater risks or uncertainties in using a biosimilar product than an innovator's product. For example, there exists the potential for a biosimilar to exhibit immunogenicity problems that were not detected in clinical trials and do not occur with the innovative product, and it requires that biosimilars undergo post-marketing monitoring like that required for new innovative biologics. It is critical that user fee resources be made available to continue to properly evaluated biosimilars in the post-market context.

J. Other Key Implementation Issues

Labeling

Unlike the Drug Price Competition and Patent Term Restoration Act of 1984 ("Hatch-Waxman") – where the same labeling, with very minor exceptions, is required for a generic drug as for the reference product[8] – BPCIA does not expressly address labeling for biosimilars. Moreover, the EMA guidelines have been relatively silent on the labeling requirements for biosimilars, and Health Canada has provided helpful, but somewhat limited, guidance on the matter. Thus, labeling is an issue on which FDA has the opportunity, and the responsibility, to take the lead in setting forth standards that will ensure understanding by patients and providers. BIO submits these comments in addition to our response to FDA's question C.4.

In short, the labeling requirements for biosimilars should flow from the fundamental premise of these products – that they will be similar, but not the same, as the reference product. For example, a biosimilar will be approved based on different data than the reference product and may have a different impurity profile. It is critical that the unique attributes of the biosimilar be clearly reflected in the labeling. Labeling that does not

[7] Food and Drug Administration, *Strategic Priorities 2011-1015: Responding to the Public Health Challenges of the 21st Century* (draft), September 29, 2010, p.18.

[8] Section 505(j)(2)(A)(v) of the Federal Food Drug and Cosmetic Act (FFDCA).

clearly identify the differences between a reference product and a biosimilar could be misleading to prescribers and patients.

Specifically, the labeling should clearly state – ideally in the Highlights section of the Package Insert (PI) – whether the product is a biosimilar or an interchangeable biologic. Product labeling should include a prominently-displayed standard warning regarding the risks of substituting or alternating innovator and biosimilar products in any given patient unless the product has been deemed by FDA to be interchangeable. The Clinical Studies section of the PI must reflect the data package on which the biosimilar was approved, including the nature of the clinical studies that were conducted. If the biosimilar were observed to have a different incidence or type of adverse event compared to the reference product, this information should be prominently displayed in the biosimilar's labeling. Consistent with the statutory approval standards, a biosimilar's labeling should not include claims of clinical equivalence to the reference product, *i.e.*, statements that the biosimilar can be expected to produce the same result in any given patient, unless the product has been deemed interchangeable. Additionally, the statute allows a biosimilar applicant to provide information demonstrating the safety, purity and potency of a biosimilar in one or more conditions of use for which the reference product is approved and for which the biosimilar applicant is seeking approval. The labeling of the biosimilar product should state which indications have been approved and specifically studied, and which have not in clear language that a user can understand and locate on the label. Identification of the actual indication(s) studied will provide an additional tool to inform a prescribers' selection of a biological product and prevent unsafe substitution.

Trade Secret/Confidential Information

As part of its implementation efforts, it is critical that FDA revise its existing regulation on disclosure of data and information contained in a BLA file to account for the newly-created biosimilar approval pathway. Currently, 21 C.F.R. Section 601.51(e) provides that various pieces of information contained in a biologics application are available for public disclosure "unless extraordinary circumstances are shown." This regulation was based upon the Agency's view in the 1970s that such information was not competitively sensitive given the inability of any subsequent biological product applicant to reference such data for its own "me too" biologic.[9]

With the advent of the subsection (k) approval pathway for biosimilars, the rationale underlying this regulation is no longer current or accurate. FDA thus should harmonize its disclosure regulations for drugs and biologics, such that information in a BLA is not available for public disclosure. Notwithstanding the current practice of the Agency – which as we understand does not actually release such information anyway – this technical correction to existing regulation is an important part of ensuring adequate protection of a biological innovator's proprietary data.

In addition, it is important for FDA to protect against any direct or indirect disclosure of information contained in the reference product BLA, or for that matter, any 351(k) application, to any third parties. Disclosure can take several forms. The clearest form

[9] 39 Fed. Reg.44602, 44641 (Dec. 24, 1974).

would be sharing the information in an approved application with another applicant seeking approval of a competitor product, and the Agency should continue to take appropriate measures to assure this does not occur in meetings or correspondence with such other applicants. Other forms of disclosure are sometimes more difficult to monitor and manage and might take the form of asking "intelligent questions" that disclose to competitors of the holder of a prior product license the type of study design, or analytic test, or other proprietary method that might be important to assuring purity, potency or safety of a biologic. The Agency should ensure that it has in place policies and review mechanisms to help prevent this second type of inadvertent disclosure so that the incentive to compete and file applications for additional products is not diminished.

FDA Reliance on Reference Product BLA

The biosimilars law creates an abbreviated approval pathway by which the testing needed to establish safety and effectiveness is presumably reduced for a sponsor seeking approval of a biosimilar product. If certain requirements are met, approval of a biosimilar can be based, to some degree, on FDA's prior finding of safety and effectiveness for the reference BLA. However, in approving a 351(k) application, FDA may rely only on publicly available information about the reference product, including the finding of safety and effectiveness. This conclusion is dictated by both the clear language of the biosimilars statute, as well as decades of well-established FDA legal and administrative precedent.

The biosimilars law makes clear that the data and information required for approval of a biosimilar must be contained completely within a 351(k) application. An application "shall include," as FDA deems necessary, the following information:

- Data from analytical studies demonstrating that the proposed product "is highly similar to the reference product notwithstanding minor differences in clinical inactive components;"
- Data from non-clinical studies, including an assessment of toxicity;
- Clinical study data, including assessment of immunogenicity and PK or PD, demonstrating the proposed product is safe and effective in one or more conditions of use for which the referenced product is licensed, and for which approval is sought;
- Information demonstrating that the proposed product uses the same mechanism of action (to the extent it is known) as the reference product for the proposed conditions of use;
- Information demonstrating that the proposed conditions of use were previously approved for the reference product;
- Information demonstrating that the proposed product has the same route of administration, dosage form, and strength as the reference product;
- Information demonstrating that the facility in which the proposed product is manufactured, processed, packed or held meets standards intended to ensure the product's safety, purity and potency;
- Publicly-available information about FDA's previous determination that the reference product is safe, pure, and potent; and

- Any additional information supporting the application, including publicly available information regarding the reference or another biologic.[10]

FDA shall license the proposed product if, *inter alia*, "the information *submitted in the application* . . . is sufficient to show that the biological product . . . is biosimilar to the reference product."[11]

Accordingly, it is the information in the 351(k) application itself – and not any information in the reference product BLA – that must be the basis for FDA's decision. Had Congress intended to allow FDA to rely on non-publicly available information in the reference product BLA in determining whether to approve a 351(k) application, Congress would have stated so in the statute. One prior biosimilars bill considered by Congress would have explicitly allowed FDA to base an approval decision on the biosimilar application "and any other information available to [FDA], including information in the application for the reference product."[12] But such a provision was not adopted into the final law. Indeed, as noted above, Congress twice in the final statute referred explicitly to only "publicly-available" information. Accordingly, in implementing this new law, FDA should make clear that the Agency's employees may not rely on any data or information in, or derived from, the reference product BLA to determine whether the biosimilar applicant has met the showing required for approval under the statute.

In this regard, FDA should rely on the precedent established in the Agency's interpretation and implementation of analogous Hatch-Waxman provisions**.** In certain respects, a 351(k) application may be analogized to a 505(b)(2) NDA or an ANDA. In both Hatch-Waxman and BPCIA, the statute allows a follow-on product sponsor to benefit from FDA's previous approval of a product to which a proposed product claims to be similar (or the same as, in the case of a generic product). Hatch-Waxman and BPCIA also both reflect a balancing of interests – encouraging the development of innovator products, while also providing an abbreviated approval path for lower cost alternatives and preventing unnecessary preclinical or clinical trials.[13] Given that both statutes allow follow-on product sponsors to similarly "leverage" prior product approvals, the limitations FDA has recognized in implementing Hatch-Waxman should similarly apply in the context of biosimilars.

FDA has said that a generic applicant "relies solely on the previous finding of safety and effectiveness for the listed drug,"[14] and "a 505(b)(2) applicant may rely on FDA's finding

[10] Section 351(k)(2)(A)(i), (iii)(I) of the Public Health Service Act (PHSA).
[11] Section 351(k)(3)(A)(i) of the PHSA (emphasis added).
[12] H.R. 1427 (111th Congress) § 3(a)(2) (adding proposed PHSA 351(k)(5)(A)).
[13] *See, e.g.*, Woodcock, *et al.*, *The FDA's assessment of follow-on protein products: a historical perspective*, Nature Reviews, 2007 (Hatch-Waxman reflects "FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources in the drug development and approval processes and avoiding ethical concerns associated with unnecessary duplication of human or animal testing."); Citizen Petition Response, Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408 (Oct. 14, 2003) at 14 (hereinafter 505(b)(2) Response) at 3-4 ("The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health.").
[14] 505(b)(2) Response at 14 .

of safety and effectiveness for a listed drug only to the same extent an ANDA applicant may rely on such a finding."[15] This "permits [an] ANDA or 505(b)(2) applicant to rely on the fact that FDA found a drug product with certain characteristics to be safe and effective and, in the case of a 505(b)(2) applicant, to target its studies to prove how changes from this previously approved drug product also meet FDA's safety and effectiveness standards."[16] There are important limitations, however, on the nature and extent of the permitted reliance: "Although reliance on an FDA finding of safety and effectiveness for an NDA is certainly indirect reliance on the data submitted in the original NDA, reliance on the conclusions supported by that data is not the same as manipulating those data to reach new conclusions not evident from the existing approval."[17]

BIO is likewise aware that FDA has told sponsors seeking approval of 505(b)(2) NDAs that the 505(b)(2) approval pathway only allows reliance on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling of the reference product. Finally, the agency unambiguously has recognized that "[r]eliance on FDA's conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant – or to the public – of the data in the listed drug's NDA."[18] As noted above, inappropriate disclosure in this context can take many forms, and it is FDA's responsibility to guard against these possibilities.

FDA should make clear that these principles and rules, applicable in the context of follow-on products for small molecule drugs, likewise apply to review and approval of biosimilar products. The rules and principles governing Agency reliance on prior findings of safety and effectiveness in the Hatch-Waxman context have been articulated by FDA primarily in Citizen Petition responses, as well as in speeches, court proceedings, and through other informal pronouncements. This *ad hoc* approach has made the rules difficult to implement,[19] and has led to confusion and a lack of transparency that has been acknowledged by the Agency.[20] Accordingly, a regulation is necessary to provide clarity

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[15] *Id.* at 10.
[16] Citizen Petition Response, Docket Nos. 2004P-0231, 2003P-0176, 2004P-0171, and 2004N-0355 (May 30, 2006) (hereinafter Omnitrope Response) at 15.
[17] 505(b)(2) Petition Response at 10, n.14.
[18] Omnitrope Response at 15.
[19] *See e.g.*, FDA's review of 505(b)(2) NDA submitted by Dr. Reddy's Laboratories for an amlodipine maleate tablet, relying on Pfizer's Norvasc® (amlodipine besylate) Tablets as the reference product. In the course of litigation following approval of the Dr. Reddy's product, FDA discovered that one of its "first line reviewer[s] made reference to certain studies of Pfizer's" in review of Dr. Reddy's application. The Agency promptly moved the court for a stay of the proceedings. "In light of this discovery," the Agency wrote, "FDA determined that it should reevaluate whether the approval of [Dr. Reddy's 505(b)(2) application] was based upon data from appropriate sources." *Pfizer, Inc. v. FDA*, 1:03-cv-02346-RCL (D.D.C.), Motion for Stay of Proceedings (Docket Item 8) at 3.
[20] *See e.g.*, Dickinson's FDA Webview, *"When and How Can FDA Share Drug-review Knowledge?"* (April 16, 2004) , statement of Office of New Drugs Deputy Director Sandra Kweder, M.D., acknowledging the difficulty of Agency personnel having proprietary or trade secret information about one applicant's product that influences discussions with (or requirements imposed on) another applicant, but having to take care not to share the information. According to Dr. Kweder,

> It is always a challenge for us . . . to explain our thinking. . . . We appear cagey and arbitrary (to sponsors) because we can't divulge how we know. . . . It's part of the challenge that we have and we're in a position, unfortunately, that more information

for the industry and FDA and facilitate compliance with legal requirements. FDA should address, through the regulatory process, the rules under which reviewers shall operate with respect to the review of biosimilar applications. These rules should clearly articulate the limited nature of the reliance permitted under BPCIA. Such a statement should be adopted as a regulation, so that it is binding on industry and the Agency, and should, among other protections, state that:

- All information necessary for approval of a 351(k) application must be contained within the biosimilar application. The Agency may not rely on any information in or derived from the reference product BLA.
- The Agency may not share any information in the reference product BLA with the biosimilar applicant that would otherwise not be publicly available.
- The Agency may not manipulate any data in the reference product BLA for purposes of supporting the biosimilar application.

Such a regulation would comport with the plain language of the statute, and reflect the balance of reference and biosimilar product sponsor interests that Congress incorporated. Moreover, it would provide clarity and greater certainty to the process, facilitate consistency within the Agency, enhance compliance with statutory and constitutional requirements, and allow industry (both reference and biosimilar product sponsors) to make informed decisions regarding development of reference and biosimilar products. These considerations are particularly important given that, unlike the review of generic drugs, review of biosimilar applications will be undertaken by the same FDA review division – and perhaps even the same individual reviewers that reviewed the reference BLA.

Avoiding Evasion of the 351(k) Pathway

FDA also should address in its implementing regulations the need to ensure that biosimilar applicants are not permitted to evade the careful balancing of innovator and biosimilar applicant rights contained in the new subsection (k) pathway. BIO believes that FDA should not allow a sponsor to choose to submit a BLA under Section 351(a) unless it fully meets the data requirements for an innovator product. Doing otherwise would eviscerate the protections for sponsors of first-generation biological products provided by Congress, undermining the careful balance of benefits and burdens that the statute reflects.

FDA has, for a long time, consistently interpreted Section 351(a) to require a full complement of original data to demonstrate a product's safety, purity, and potency. That is why the new biosimilars law was enacted: to establish circumstances under which a sponsor could bypass the requirements of Section 351(a) when a complete set of original data is not needed due to pre-existing data on a highly similar biologic previously approved by the Agency. Where a sponsor seeks to abbreviate its testing program through reliance on FDA's prior findings of safety and efficacy for a highly similar existing product, FDA should not accept an application for filing under 351(a). To do so

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> really facilitates a more scientific approach, and yet there are holds on sharing that information . . . . It's something we have to continue to work with you on.

would essentially result in a biosimilar applicant receiving the benefits of the new abbreviated pathway without having to bear the concomitant burdens, *e.g.*, waiting for the expiration of exclusivity or complying with other provisions designed to protect innovator rights.

Accordingly, BIO believes that FDA must establish clear rules on what types of applications will be reviewed under 351(k) versus 351(a).

Ensuring the Protection of Innovator Statutory Rights to Biosimilar Information

BIO members believe that FDA has an important role in the implementation of the Act's patent resolution and information exchange process. Specifically, FDA should require that the subsection (k) applicant formally certify that it has or will comply with the BPCIA provisions requiring the biosimilar applicant to timely share its BLA and manufacturing process information with the reference product's sponsor. The Agency need not police the entire patent exchange process, but a certification procedure is necessary to give effect to this integral part of the statutory scheme. Without such notice and information exchange, the innovator would not be in a position to adequately protect its proprietary rights as set forth in the statute, upsetting the careful statutory balance of innovator and biosimilar applicant rights. Certification by the subsection (k) applicant is a simple and nonintrusive requirement that FDA can impose to effectuate these statutory rights, without undue burden on the Agency or applicants, and without the Agency becoming involved in the process itself.

Additionally, FDA should clarify processes for service, and designation of recipients, of the subsection (k) application, related information, and subsequent patent lists and statements. Requiring the parties to have such processes in place at the inception of the information exchange and patent resolution pathway will facilitate the timely and smooth operation of the pathway without requiring Agency intervention.

Finally, FDA should clarify the applicable procedures that apply to the exchange of information contained in a supplement to a subsection (k) application that is filed after initiation of the patent resolution pathway.

CONCLUSION

BIO appreciates this opportunity to comment on the Agency's Approval Pathway for Biosimilar and Interchangeable Biological Products. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Executive Vice President, Health
Biotechnology Industry Organization

for questions regarding legal matters, please contact:
Sandra J.P. Dennis
Deputy General Counsel for Healthcare
Biotechnology Industry Organization