DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

OCT 13 2016

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the February 4, 2016, hearing before the Committee on Energy and Commerce, entitled "Examining Implementation of the Biologics Price Competition and Innovation Act." This letter is a response for the record to questions posed by Members of the Committee.

If you have further questions, please let us know.

Sincerely,

Dayle Cristinzio
Acting Associate Commissioner
for Legislation

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Enclosures (2)

We have restated your questions below in bold, followed by our responses.

The Honorable Marsha Blackburn

1. **Dr. Woodcock, the agency has posted online documents from the Zarxio review that suggest the agency and applicant agreed in November 2013 that the Zarxio labeling should be the same as its reference product labeling, even though the February 2012 draft guidance publicly stated the opposite. Is the agency departing privately from any other advice set forth publicly in its draft or final biosimilar guidance documents?**

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

FDA's draft guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did not address labeling issues in its final guidance[1] because prior to finalizing this guidance, FDA announced it would issue a draft guidance on labeling for biosimilar products.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The guidance further recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product, with a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

2. **Dr. Woodcock, why did the agency reverse its decision that biosimilar labeling clearly identify a product as biosimilar and/or interchangeable? How does the agency justify this change with overwhelming multi-stakeholder support for transparent labeling and the agency's original position that transparent labeling was "necessary?"**

Please see our response to your first question above.

3. **Dr. Woodcock, at least seven biosimilar applications are pending at the FDA. Does FDA plan to continue taking approval actions on applications without disclosing its labeling policy to the public?**

While guidances are an important tool for industry, the law expressly states that there is no requirement to issue guidance before reviewing or taking an action on a biosimilar

[1] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

application. FDA makes decisions based on scientific data and if we have the data to support an approval, then we can make a decision regardless of whether we've issued guidance. On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. In addition, we have issued four final guidances and four additional draft guidances for industry related to implementation of BPCI Act.

4. **Dr. Woodcock, a number of stakeholders have called for more open public discussion of the complex scientific and policy issues surrounding interchangeability. What steps does FDA plan to take to address these calls for greater public discussion of the open questions on interchangeability? For example, does the agency plan to hold a public meeting, such as a Part 15 hearing, to receive input on these issues from all interested stakeholders?**

FDA intends to issue draft guidance on *Considerations in Demonstrating Interchangeability With a Reference Product*. FDA will follow its good guidance practices for finalizing this draft guidance document, which includes providing an opportunity for public comment before it is finalized.

5. **Dr. Woodcock, GAO recently reported on deficiencies in the FDA's post-marketing safety (pharmacovigilance) program. Dr. What assurances do we have that the agency has the capability to quickly and effectively conduct better pharmacovigilance for highly immunogenic, complex medicines like biosimilars?**

Robust postmarketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar products. There are many factors that influence postmarketing safety monitoring considerations, including but not limited to, any particular safety or effectiveness concerns associated with the use of the reference product and other products in the class, data on the proposed product obtained during its development and clinical use (if marketed outside the United States), and the specific condition(s) of use and patient population(s).

Moreover, the Centers for Medicare and Medicaid Services (CMS) and FDA have developed and implemented an approach to use manufacturer-specific modifiers, to facilitate pharmacovigilance for biological products that share a billing code.

<u>The Honorable John Shimkus</u>

1. **I have heard concerns from stakeholders following the first biosimilar approval regarding the information that was contained in the product label. My understanding is that a cut and paste label from the reference product was applied to the biosimilar that didn't even contain the simple statement that the product was approved as a biosimilar. This decision seems to be in stark contradiction to the original guidance that your agency released back in 2012, where you called for clear statements identifying the product as biosimilar and if it is interchangeable or not. Can you comment on when you will be releasing draft guidance in this**

important area and provide some insight as to the scientific rationale behind the change in policy from 2012 to when you approved the first biosimilar last Spring?

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

FDA's draft guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did not address labeling issues in its final guidance[2] because prior to finalizing this guidance, FDA announced it would issue a draft guidance on labeling for biosimilar products.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The guidance further recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product, with a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

2. **I want to reference two surveys, that I am going to submit to the record, conducted last year by the Alliance for Safe Biologic Medicines (ASBM). One is a physician survey (done before the Zarxio approval) and one is a pharmacist survey. In total, over 800 healthcare professionals from a variety of medical backgrounds were asked questions regarding what they thought would be important to include on a biosimilar label. Without getting into specifics, it was overwhelmingly clear that physicians and pharmacists value transparency within product labeling so that they have a strong clinical understanding of the medicines they are prescribing. If our goal is to ensure the penetration of these products into the marketplace, shouldn't we enact a transparent labeling policy that creates confidence within the healthcare community?**

Health care professionals should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients. Health care professionals are advised to review the labeling (prescribing information) of the biosimilar product to determine which conditions of use and routes of administration the biosimilar was approved for. A biosimilar product can be approved by FDA for some or all of the same uses as the FDA-approved reference product that the biosimilar was compared to, and prescribed by a health care professional as appropriate. On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA

[2] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product.

3. **In August 2015, FDA released draft guidance outlining their position on a naming structure for biological products. Appropriately, critical safety and pharmacovigilence considerations were addressed to ensure the safety of patients receiving these products. When describing your decision to include a four digit suffix following the core name of the biologic, there remained some outstanding questions that you presented back to stakeholders around interchangeability and whether there should be meaning associated with the suffix. I can understand on a cost basis why some people might want a random suffix, but I struggle to understand why the FDA, on scientific grounds, wouldn't want healthcare stakeholders to know or associate a meaningful suffix that points to a manufacturer or some other type of information. Can you comment on that? Also, with the recent WHO releasing their thoughts on naming, does the FDA feel the need to harmonize with them on a more global view on naming?**

FDA recently issued draft guidance on *Nonproprietary Naming of Biological Products*, which describes FDA's approach to designating the proper name of a biological product. FDA is following its good guidance practices for finalizing this draft guidance document, which includes providing an opportunity for public comment before it is finalized.

FDA is working closely with the World Health Organization (WHO) to understand the technical aspects of its proposed naming policy. There are similarities and differences between the FDA's proposed naming convention and the WHO proposal to assign a four-letter "biological qualifier" to each biological substance to complement its international nonproprietary name (INN).

In the Federal Register notice announcing the availability of the draft guidance, FDA requested comment on how biological qualifiers generated by WHO should be considered in the determination of FDA-designated proper names for the biological products within the scope of the guidance if WHO adopts a Biological Qualifier proposal. FDA also requested comment on whether the format of the suffix should be unique to each product or shared by those products made by a single license holder, whether or not the suffix should be devoid of meaning, and questions related to the naming of interchangeable products. FDA will carefully consider all comments that have been submitted to the public docket.

6. **Under current law, a new biological product can be brought to market either by being approved as a new drug or by being licensed as a biological product.**

    a. **How, if at all, does a manufacturer's decision to use one pathway or the other affect (1) FDA's premarket review of the product, (2) the postmarket obligations of FDA and the manufacturer, and (3) the ability of another manufacturer to use that product as a reference product in a subsequent biosimilar application?**

    Although the majority of biological products have been licensed under section 351 of the Public Health Service Act (PHS Act), some protein products historically have

been approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) changed the statutory authority under which certain protein products will be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)." Section 7002(e) of the BPCI Act requires that a marketing application for a "biological product" must be submitted under section 351 of the PHS Act. This requirement is subject to certain exceptions during a 10-year transition period ending on March 23, 2020, which provide that an application for a biological product may be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product class for which a biological product in such product class was approved under section 505 of the FD&C Act not later than March 23, 2010. However, an application for a biological product may not be submitted under section 505 of the FD&C Act if there is another biological product approved under section 351(a) of the PHS Act that could be a "reference product" if such application were submitted under section 351(k) of the PHS Act. On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4) of the BPCI Act).

FDA has taken measures to minimize differences in the review and approval of products approved in Biologics License Agreements (BLAs) under section 351 of the PHS Act and products approved in New Drug Applications (NDAs) under section 505(b)(1) of the FD&C Act (see section 123(f) of the Food and Drug Administration Modernization Act of 1997 (FDAMA)). FDA has been working to ensure that consistent scientific standards are applied to "stand-alone" marketing applications for biological products irrespective of whether the application is submitted under the FD&C Act or under the PHS Act.

The BPCI Act provides that the term "reference product" means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) BLA. During the 10-year "transition period" ending on March 23, 2020, a biological product approved under section 505 of the FD&C Act may be a listed drug relied upon in an application submitted under an abbreviated approval pathway under the FD&C Act (e.g., a 505(b)(2) application).

b. Please identify each biological product currently on the market that has been approved as a new drug under 21 U.S.C. § 355(b). Has any of these products also been licensed as a biological product under 42 U.S.C. § 262(a)? If so, which one(s)?

Although the majority of biological products have been licensed under section 351 of the PHS Act, some protein products historically have been approved under section 505 of the FD&C Act. These products include, for example, the following currently marketed products: chorionic gonadotropin products, desirudin products, follitropin products, urofollitropin products, menotropins products, hyaluronidase products, imiglucerase products, insulin products, insulin mix products, insulin analog

products, mecasermin products, pancrelipase products, pegademase products, pegvisomant products, sacrosidase products, somatropin products, taliglucerase alfa products, velaglucerase alfa products, and thyrotropin alfa products.

At this time, none of these biological products has been licensed under section 351 of the PHS Act.

c. Does FDA currently receive applications for new biological products under both pathways? How has the relative frequency with which the respective pathways are used changed over time? To the extent there have been changes, to what does FDA attribute them?

FDA currently receives applications for new biological products under section 351(a) of the PHS Act or, if the proposed product falls within the exception described in section 7002(e)(2)-(e)(3) of the Biologics Price Competition and Innovation Act of 2009, under section 505 of the FD&C Act. FDA does not track the number of applications submitted under section 505 of the FD&C Act by whether the proposed product is a biological product, so FDA cannot address the relative frequency with which use of the respective pathways has changed over time for such products.

d. Please (1) identify any follow-on biological products that have been approved as generic drugs, and (2) explain how these products satisfied the statutory requirement that a generic drug be identical its reference product, given the complexity and variation inherent in the development of follow-on biological products.

FDA approved two related abbreviated new drug applications (ANDAs) under section 505(j) of the FD&C Act for a menotropins product in 1997. At that time, the Agency acknowledged the isoform variation in the active ingredient, but concluded that it was not clinically significant for the product's intended uses and therefore did not preclude a finding of "sameness" for purposes of section 505(j) of the FD&C Act. The approval was the subject of a decision by the U.S. Court of Appeals for the D.C. Circuit, which found that the "FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court" (Serono Laboratories, Inc. v. Shalala, 158 F.3d 1313, at 1320 (D.C. Cir. 1998) (internal citations omitted)).

FDA regulations implementing section 505(j) of the FD&C Act provide that an ANDA is suitable for consideration and approval if the proposed generic drug product is the "same as" the reference listed drug, meaning, among other things, "identical in active ingredient(s)" (see 21 CFR 314.92(a)(1)).

7. In February 2012, FDA published a draft guidance document in which it stated that a biosimilar's labeling "should include all the information necessary for a health

professional to make prescribing decisions," including a "clear statement" (1) advising that the product is a biosimiar, and (2) explaining whether the product has been approved as interchangeable with its reference product. But FDA subsequently approved a biosimilar without requiring either statement in its labeling, then deleted this requirement when it finalized the draft guidance in April 2015. Several months later, FDA stated in response to a question by members of this committee that health care professionals instead can find this information in the "Purple Book," FDA's published list of biological products.

e. Does FDA continue to believe, as it stated in its 2012 draft guidance, that information about whether a product is a biosimilar, and whether patients may safely switch between the biosimilar product and its reference product, is "necessary for a health professional to make prescribing decisions"?

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

FDA's draft guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did not address labeling issues in its final guidance[3] because prior to finalizing this guidance, FDA announced it would issue a draft guidance on labeling for biosimilar products.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. The draft guidance also recommends a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

f. Under the Food, Drug, and Cosmetic Act, a biological product must include "adequate directions for use" in its labeling. Does FDA consider the directions for a biosimilar product to be adequate if (1) they do not identify the product as a biosimilar, or (2) they do not describe whether a patient may safely switch between the biosimilar product and its reference product? Why or why not?

Healthcare professionals should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients. Healthcare professionals are advised to review the labeling (prescribing information) of the biosimilar product to determine the conditions of use for which

[3] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

the biosimilar was approved. A biosimilar applicant may request licensure for some or all of the same uses as its FDA-approved reference product.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. The draft guidance also recommends a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

g. Does the FDA consider the Purple Book to be a part of a biological product's labeling?

FDA created the "Purple Book" on its own initiative to provide a convenient source of information regarding licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Unless the Purple Book accompanies a specific biological product, it is not considered part of that product's labeling.

h. Are health care professionals required to consult the Purple Book when making prescribing decisions? What information has FDA reviewed regarding when, and to what extent, health care professionals actually consult the Purple Book?

Healthcare practitioners should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients. Healthcare practitioners are advised to review the product labeling (prescribing information) to determine the conditions of use for which the product was approved; the Purple Book is not intended to be a resource for this information.

The BPCI Act defines an interchangeable product to mean that the product has met the statutory standard for interchangeability and may be substituted for the reference product (e.g., by a pharmacist) without the intervention of the healthcare provider who prescribed the reference product. The listing of interchangeable products under the reference product to which interchangeability was demonstrated will make it easier for pharmacists to consult the Purple Book for substitution decisions.

FDA is conducting qualitative research with physicians, nurse practitioners and pharmacists to learn more about their perspectives on biosimilars, their trusted sources of information, and the kinds of information that they would like to receive. Additionally, we are developing a continuing medical education (CME) course for prescribers about biosimilars. FDA is working to develop communication materials to educate consumers and health care professionals. These will be posted on the FDA biosimilar web pages and distributed to stakeholders through email and conferences.

8. **In April 2015, FDA indicated in a guidance document that it may allow a biosimilar to be marketed to treat diseases and conditions for which it has not been studied, if the reference product has been approved for those indications and the biosimilar's safety and potency for those indications can be inferred—or "extrapolated"—from studies for other indications.**

    i. **If a product is approved for both studied indications and extrapolated indications, does FDA intend to differentiate between the two types of indications in the product's label? If not, how does it intend to communicate these differences to patients and health care providers?**

FDA does not intend to differentiate between indications that were directly studied and those supported through extrapolation in product labeling if the reference product has been approved for these indications. FDA undertakes a rigorous and thorough evaluation to ensure that a biosimilar product meets the Agency's standard for approval. When FDA approves a biosimilar product, it has determined that the product meets the Agency's standard for approval for all indications for which the biosimilar product is approved, including any approved indications that were supported by extrapolation, and has been demonstrated to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency.

FDA has issued final guidance outlining the issues that an applicant should consider when providing a scientific justification for extrapolating clinical data sufficient to demonstrate safety and effectiveness in one condition of use to support a determination of biosimilarity in one or more additional conditions of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for which licensure is sought; this may include:
    - The target/receptor(s) for each relevant activity/function of the product;
    - The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
    - The relationships between product structure and target/receptor interactions;
    - The location and expression of the target/receptor(s).
- The pharmacokinetic and bio-distribution of the product in different patient populations (relevant pharmacodynamic measures also may provide important information on the mechanism of action);
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities); and

- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Differences between tested and extrapolated conditions of use with respect to the factors described above do not necessarily preclude extrapolation, but differences need to be addressed. The applicant should ensure that the totality of the evidence submitted, including scientific justification for extrapolation, supports its approach.

To determine which indications have been approved for a biosimilar product, health care professionals are advised to review the labeling – prescribing information – of the biosimilar product. On March 31, 2016, FDA issued a draft guidance on labeling for biosimilar products.

j. What postmarket surveillance will FDA require for extrapolated indications? How, if at all, will the requirements vary by circumstance?

Robust postmarketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar products. There are many factors that influence postmarketing safety monitoring considerations, including but not limited to, any particular safety or effectiveness concerns associated with the use of the reference product and other products in the class, data on the proposed product obtained during its development and clinical use (if marketed outside the United States), and the specific condition(s) of use and patient population(s).

When FDA approves a biosimilar product, it has determined that the product meets the Agency's standard for approval for all indications for which the biosimilar product is approved, including any approved indications that were supported by extrapolation and has been demonstrated to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency.

k. Under what circumstances would FDA rescind approval for an extrapolated indication? What procedural requirements and evidentiary standards would apply?

When FDA approves a biosimilar product, it has determined that the product meets the Agency's standard for approval for all indications for which the biosimilar product is approved, including any approved indications that were supported by extrapolation and has been demonstrated to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency. FDA does not envision a difference in the procedural requirements or evidentiary standards for withdrawing approval of a 351(k) BLA as compared to a 351(a) BLA.

9. Please identify the requirements for manufacturing practices and inspections that apply to manufacturers of biological products, including biosimilars.

l. Does the nature or frequency of establishment inspections differ between small molecule drugs and biological products? If so, how?

The nature of inspections of small molecule drug and biologics product inspection do not differ in approach as each inspection is conducted in accordance with a Compliance Program, which provides instruction on the scope and direction of the inspection.

All biological products and drug products must be manufactured in conformance with current Good Manufacturing Practice (CGMP) requirements as described in section 501(a)(2)(B) of the FD&C Act and the regulations in 21 CFR parts 210 and 211. Biological products are also subject to the applicable requirements in 21 CFR parts 600-680. There are two main types of establishment inspections that are performed for manufacturers of biological products: premarket (pre-approval/pre-license) inspections; and, postmarket (surveillance) inspections. Premarket inspections are performed during the review of a BLA or NDA or supplement, and are part of the assessment used to determine whether to approve the application. The purpose of premarket inspection is to assess the manufacturing process and its conformance to CGMP requirements; data integrity; and, the readiness of the establishment to manufacture the product. An establishment must operate in conformance with CGMP and all other applicable standards and should be ready to manufacture the product in a manner described in the application before approval is granted. Postmarket inspections are performed to determine whether inspected firms are operating in compliance with CGMP requirements and other applicable regulations, and if not, to document the evidence for appropriate follow up actions. Postmarket inspections may be performed as surveillance inspections, or for a variety of other reasons, including in response to information obtained by FDA, such as complaints or adverse events. The initiation of a premarket inspection is associated with the submission of a BLA or NDA or supplement. During the course of the review of the BLA or NDA or supplement, a risk based decision is made as to which sites need an inspection relating to the product under review. This decision is based on the assessment of the relative risk and complexity of the product being manufactured as described in the application combined with the history of inspections that have been performed by FDA at that manufacturing facility. If an inspection is warranted, it is performed during the review of the application.

The frequency of postmarket inspections for small molecule drug products and biological drug products is established based on a variety of risk factors. The Food and Drug Administration Safety and Innovation Act, Section 705, requires that the frequency be based on the known safety risks of such establishments, including the compliance history, recalls, inherent risk of the drug, the inspection frequency and history of the establishment, foreign government inspections, and other criteria deemed necessary and appropriate by the Secretary.

m. Is the manufacturer of a biological product subject to requirements that differ from those applicable to the manufacturer of a small molecule drug?

All FDA-approved drugs and biological products have met the Agency's standard for approval and have been determined to be safe and effective under the conditions of

use described in approved product labeling. The requirements for biological products generally are the same as those for small molecule drug products.

However, there are some different requirements as drugs are approved under the FD&C Act whereas biologics are licensed under the PHS Act. Biological products are subject to the applicable requirements in 21 CFR parts 600-680, in addition to the CGMP requirements generally applicable to both small molecule drugs and biological products.

n. If a biological product is approved as a new drug rather than licensed as a biological product, does it affect which requirements apply?

All biological products and drug products must be manufactured in conformance with CGMP requirements as described in section 501(a)(2)(B) of the FD&C Act and the regulations described at 21 CFR parts 210 and 211. Additionally, biological products licensed under the PHS Act must meet the applicable requirements in the PHS Act and the regulations described in 21 CFR 600-680.

o. Are any biological products currently being imported from India or China? Given recent concerns regarding the quality of finished drugs and ingredients manufactured in those countries, and the complexity of biological products relative to small molecule drugs, what is FDA doing to ensure the safety of any biological products imported from those countries?

Our response is inclusive of any establishments that manufacture the drug substance and drug products under licensed BLAs and approved NDAs for biological products, and does not include investigational products or non-application products.

Amphastar Pharmaceuticals, Incorporated, has an approved NDA for *Hyaluronidase Injection USP* in which the drug substance is currently being manufactured by Amphastar Nanjing Pharmaceuticals, Incorporated, in Jiangsu, China. The drug substance is imported into the United States in order to manufacture the finished product.

The other drug substance manufacturer that is approved for Amphastar's application is Shanghai Number 1 Biochemical Pharmaceutical Company, Limited (SBPC) in Shanghai, China. Although the facility is approved for that application, the *Hyaluronidase* drug substance from SBPC is not currently allowed entry into the United States due to an Import Alert that has been in effect since 2009. This Import Alert requires Detention Without Physical Examination for all Active Pharmaceutical Ingredients manufactured at this particular facility because the methods and controls used in its manufacture and control of drug products do not appear to conform to current Good Manufacturing Practice.

There are additional establishments in China and India that have been proposed in applications for biological products as manufacturing facilities for drug substances and drug products. However, these applications are pending or have otherwise not been approved or licensed for marketing in the United States. Therefore, such

products would not be imported for the purpose of commercial distribution within the United States at this time.

All registered drug manufacturing facilities are subject to inspection, with inspection frequency determined on the basis of risk to patients. FDA employs a highly trained inspectorate, which is skilled in uncovering failures in compliance with good manufacturing practices. Whenever FDA investigators find product quality issues that potentially implicate drug safety and efficacy, the Agency takes appropriate action, which could include issuing a warning letter or import alert, or taking other enforcement action. All FDA-approved drugs delivered to patients in the United States are subject to the same high standards, regardless of country of origin.

10. Please describe what steps FDA has taken, and plans to take in the future, to educate patients and health care professionals about the risks and benefits of biosimilars. What has it spent on such education efforts to date, and what funding is necessary for future education efforts? How will FDA's education efforts balance the need to promote health care savings through increased use of lower-cost products against the need to ensure that patients and health care professionals understand any relevant risks?

FDA has a multi-phase plan for communicating with stakeholders about biosimilar products. The first phase of communication is to lay a solid foundation with basic definitions and descriptions about biosimilar products that health care professionals and consumers can easily understand and adopt.

Concurrent with the approval of Zarxio, the first biosimilar product in the United States, FDA updated its website to provide more information about biosimilar products, including pages specifically for consumer[4] and health care professional[5] audiences. The content includes definitions of biosimilar products and interchangeable products, information on how health care professionals can prescribe these products, and the differences between biosimilar products and generic drugs.

FDA also released a Consumer Update[6] that outlined the basic concepts of biosimilar products.

FDA provided notification about the updated website and Consumer Update to many stakeholder and health care professional organizations and encouraged dissemination to their members and patients. FDA plans to communicate information in various formats to consumers and health care providers as more biosimilar products are approved and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability.

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[4] *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm.*

[5] *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm.*

[6] *http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm.*

Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to maximize health care provider and consumer confidence in this new category of products.

11. Under current law, several important responsibilities for regulating drugs (including biological drugs) are assigned to the U.S. Pharmacopeial Convention (USP), a nonprofit organization that publishes an official compendium of drugs. For example, a drug must meet the standard of identity described in the USP compendium, and generally must print the scientific name selected by USP—called an "established name"—on its label.

p. How, if at all, do USP's responsibilities and activities differ between biological products and small molecule drugs? Does FDA believe that USP's current role with respect to biological products is appropriate?

It is FDA's view that enforceable monographs and chapters are not beneficial for biological products. The vast majority of U.S. Pharmacopeial Convention (USP) monographs relate to small-molecule chemically-synthesized drugs. These products generally are not complex and can be fully characterized using widely available analytical tests. On the other hand, biological products are generally diverse and complex, with a large number of attributes that are evaluated using analytical and other technologies that develop and advance rapidly. Tests and assays sufficient to characterize biological products often are themselves complex, manufacturing-process-specific, and/or patented. USP has published only a few monographs for biological products, but the organization recently has initiated the development of such monographs in greater numbers. Recognizing the complexity of biological products, FDA has amended its regulations that detail manufacturing and testing requirements to remove prescriptive standards in favor of a more flexible approach in order to foster innovative technologies and facilitate approval of novel biologics including cellular and gene therapies.

FDA has significant concern that enforceable monographs for biological products may impede or delay approval of a biological product that meets the scientific requirements for approval, but does not meet the related compendia standards established by USP, an independent, non-governmental organization. For example, the BPCI Act provides FDA with the authority to approve a biosimilar product that has been shown to be "highly similar" to its reference product, notwithstanding minor differences in clinically inactive components, and that also meets other requirements in section 351(k) of the PHS Act. If a proposed biosimilar product was required to comply with same USP drug product monograph as its reference product, it effectively would require the applicant to demonstrate that its product contains the "same" drug substance as the reference product, evaluated using the same tests and assays, notwithstanding the standards set forth in the statute. We anticipate that this may complicate licensure of biosimilar (and interchangeable) products that meet the requirements of the BPCI Act, but may not comply with the provisions of the FD&C Act regarding USP compendia standards.

In addition, FDA has significant concern that enforceable biological product monographs may impede or delay innovative technologies for biological products, including improvements to already-approved products, to the extent that those improvements do not meet the related USP standards. The Agency has communicated these concerns to USP (see Enclosure A - March 2014 letter).

We anticipate that enforceable biological product monographs will be an additional, unnecessary burden on regulated industry and FDA reviewers.

q. Despite USP's statutory role in the naming of biological drugs, FDA's recent draft guidance on naming does not discuss USP. Has USP been consulted in the development of FDA's policy on naming conventions? To what extent does USP agree with the current thinking proposed in the draft guidance? To the extent USP disagrees, what are the practical implications of any disagreement?

FDA notified the USP that FDA had proposed a regulation to designate official names and proper names for certain biological products (see Designation of Official Names and Proper Names for Certain Biological Products; Proposed Rule, 80 FR 52224, August 28, 2015). FDA invited USP to submit recommendations for official names, which will have usefulness and simplicity, for the six products included in the proposed regulation. FDA also invited USP to provide recommendations and comments on any other aspect of the proposal that would designate official names and proper names for these products that would include distinguishing suffixes composed of four lowercase letters. USP submitted comments to the public dockets established for the proposed rule and the draft guidance. FDA will carefully consider all comments, including comments submitted by USP, as we determine next steps.

r. FDA's draft guidance on naming describes how to select a biological product's "proper name," which is the statutory term for a biological product's scientific name. But a biological drug's scientific name also is regulated as an "established name" under the drug statutes, and the draft is silent about how the guidance would apply to these "established name" requirements. Would a "proper name" under this guidance always be the product's "established name," or are there circumstances in which a product's "proper name" and "established name" might be different?

FDA believes that a biological product should have a single nonproprietary name.

The draft guidance, *Nonproprietary Naming of Biological Products*, described FDA's approach to designating the proper name of a biological product, which is the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act. The established name of a drug is described in section 502(e) of the FD&C Act. To the extent a biological product were considered to have an inconsistent proper name and established name, FDA would take appropriate action to ensure that a single nonproprietary name is used for the product.

12. Dr. Woodcock, does the FDA believe that it would be in the best interest of the Biosimilar pathway if the BPCIA's patent dispute provisions were interpreted as mandatory, as opposed to an optional dispute procedure that a biosimilar may choose to follow?

Section 351(l) of the PHS Act describes procedures for information exchanges and the resolution of certain patent disputes between a biosimilar applicant and the reference product sponsor. These procedures are parallel to, but separate from, the FDA review process. The BPCI Act generally does not describe any FDA involvement in monitoring or enforcing the patent information exchange described in section 351(l) of the PHS Act and does not direct FDA to provide guidance on section 351(l) of the PHS Act.

13. Is it possible that FDA might approve an interchangeable product without first issuing guidance on interchangeability?

While guidances are an important tool for industry, FDA does not need guidances to make decisions on applications for biosimilar products or interchangeable products. The BPCI Act provides that FDA may issue guidance on the licensure of biosimilar products and interchangeable products and expressly states that there is no requirement to issue such guidance before reviewing or taking an action on an application for a biosimilar product or an interchangeable product. FDA makes decisions based on relevant law and scientific evidence. If an applicant submits the data to support an approval, then, consistent with the BPCI Act, FDA can make a decision regardless of whether the Agency has issued guidance.

14. Is there anything Congress can do to help FDA speed up issuing the guidance?

FDA is diligently working to issue guidance on issues that have been identified by FDA and stakeholders as key topics of interest, including interchangeability.

15. We hear a lot of concern about consistency, or lack of consistency, across review divisions. This seems especially important regarding the willingness and ability of reviewers in different divisions to embrace the use of 21st century drug development tools – such as biomarkers and patient-reported outcomes, innovative clinical trial designs, and new statistical approaches. What are you doing to try to ensure that application sponsors can reliably get consistent advice and approaches when they bring new and creative drug development ideas to FDA, regardless of the review division with which they are working?

In the area of biosimilar and interchangeable product development, FDA formed a working group to plan and develop the Agency's approach to implementing the statute in order to ensure that the process of evaluation, review, and approval of products within this newly-defined product category will be achieved in a consistent, efficient and scientifically sound manner. The Biosimilar Implementation Committee (BIC) is a cross-center group with representation from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), and also has members from the Office of Chief Counsel and the Office of the Commissioner. In addition, FDA formed two review committees; the CDER Biosimilar Review Committee and the CBER Biosimilar Review Committee. Both groups have members from both CDER and CBER and address product-

specific review and issues relating to scientific methodology. In addition, the Therapeutic Biologics and Biosimilars Staff (TBBS) in the Office of New Drugs, CDER, is responsible for ensuring consistency in the scientific and regulatory approach reflected in recommendations to sponsors regarding proposed biosimilar development programs.

16. **The complexity and uniqueness of each biologic medicine require that FDA ensure that all biologics and biosimilars are thoroughly tested and meet the highest patient safety and manufacturing quality standards. Given the complex manufacturing process when even slight changes can cause major problems, what resources does FDA have designated to inspect biosimilar manufacturing facilities? Are FDA inspectors receiving additional, specialized training to inspect these facilities? Are there any specific differences in FDA protocol for the inspection of a biosimilar manufacturer versus a reference biologic manufacturer? A recent report in the Economic Times indicated that Indian maker of the Ramuzab an injectable biosimilar for macular degeneration produced and approved for use in India had curtailed distribution after a number of adverse events associated drug had been reported. In addition, media reports that some manufacturers in India that have had serious quality control problems identified in their manufacturing of much simpler generic drugs are planning to produce biosimilars. How many FDA inspectors are there in India who have expertise in reviewing biologics and/or biosimilars manufacturing facilities? Is this this adequate to assure patient safety?**

Currently, there are no differences in the protocol for the inspection of a biosimilar manufacturer versus a reference biological product manufacturer, as both inspections are conducted in accordance with a Compliance Program, which provides instructions on the scope and direction of the inspection.

FDA does place a high level of importance on ensuring that only high quality reference biological and biosimilar products are approved for marketing in the United States. Both the manufacturing process and the facility are critical to ensure that level of product quality. FDA has the resources to inspect biosimilar manufacturing facilities. We select individuals that are highly knowledgeable regarding the manufacturing of biological products to perform reviews of applications and premarket inspections of manufacturing facilities. By performing both roles, these individuals further enhance their knowledge of manufacturing of reference biological and biosimilar products. We have specialized training on biologics manufacturing for individuals who perform inspections of biologics manufacturers. Additionally, the more experienced investigators train less experienced investigators during the course of inspections. An experienced investigator always leads the inspection of biological products. This training and mentoring exists for both reference biological product manufacturers and biosimilar manufacturers. For postmarket inspections of biological product manufacturers, investigators with specialized training in biologics manufacturing are selected for assignments. Thus, there is assurance that investigators who perform these inspections are well trained and qualified.

Please be aware that premarket inspections of biological products are led by individuals in either CDER or CBER, who are located in Silver Spring, Maryland. These individuals travel to the location of the manufacturing facility to perform the inspection, regardless of where

such facility is located (which would include India and China). The Center inspection team invites the Office of Regulatory Affairs (ORA) and the Office of International Programs (including the China and India Offices) to participate in any overseas inspections that will be performed. These premarket inspections are performed for any BLA that is submitted to FDA. We believe that FDA's inspection resources are adequate to assure patient safety.

FDA has two investigators based in-country to perform food and drug inspections in India. However, as mentioned above, FDA does not depend only on its own investigators based in-country. In addition, often with FDA India Office detailees from ORA with biologics expertise who are there for a few months, FDA ORA personnel with specific biologics expertise travel to India for specific surveillance or other biologics inspection assignments, sometimes with experts from the Centers.

17. I understand that FDA still has not provided details on the specifics of interchangeable products; but can you tell me broadly in your mind what an interchangeable looks like?

The BPCI Act defines interchangeability to mean that the biological product has been shown to meet the statutory standards for interchangeability and may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The BPCI Act provides that FDA shall determine a proposed biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application is sufficient to show that (1) the biological product is biosimilar to the FDA-approved reference product, (2) the biological product can be expected to produce the same clinical result as the reference product in any given patient, and (3) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

18. Can the agency comment on whether the concept of finger-print like similarity at the analytical level is linked to interchangeability requirements?

FDA intends to address in guidance how comparative structural and functional characterization may contribute to the body of data and information necessary to support a demonstration of interchangeability.

19. The agency has mentioned plans to issue interchangeability guidance before the end of the year. Is this still on track and can you talk to some of the challenges around what seems to be a very scientifically complex determination.

FDA is diligently working to issue guidance on issues that have been identified by FDA and stakeholders as key topics of interest, including interchangeability. FDA anticipates issuing the biosimilar guidances listed in our guidance agenda, including guidance on demonstrating

interchangeability, within the next 12 months. While these are our best estimates, they are subject to change and factors such as workload could influence these estimates.

20. FDA has yet to release guidance on what evidence companies will be required to present to the Agency to prove they have met the requirements to receive an interchangeable designation for biosimilars. At the same time, companies are making significant advancements in how to analyze biologics with increasing precision, potentially reducing the necessity for expensive clinical trials. As the agency develops that guidance, will you leave room for future advancements in analytical technologies so that these products can be brought to market faster without unnecessary trials?

FDA intends to exercise appropriate scientific judgment in determining the data and information necessary to meet the statutory standard for interchangeability and approval by the Agency.

21. Does FDA believe that biosimilars have the potential to be different enough from the reference product to require a different label?

The labeling of a product that meets the statutory standard for biosimilarity may potentially differ from the labeling of the reference product for a variety of reasons. For example, there may be differences between the biosimilar product labeling and the reference product labeling due to differences in the applicability of certain labeling format and content requirements. One such example is that biological products approved since June 30, 2001, must have labeling that follows the Physician's Labeling Rule (PLR) format; thus, all biosimilar products but not necessarily all reference products will have labeling in PLR format. There also may be product-specific labeling differences that are necessary to inform the safe and effective use of the product but do not preclude a determination of biosimilarity.

22. As you know, many have serious concerns regarding the naming of biosimilars to provide transparency and ensure patient safety. Given recent efforts by the FDA to protect patient safety by issuing import alerts and the blacklisting of some manufacturers, has the FDA considered any labeling requirements to disclose the manufacturer and country of the origin of biosimilars?

Under current FDA regulations, all biological products licensed under the PHS Act (including biosimilar products) are required to include the name, address, and license number of the manufacturer on the package label and container label. The license holder is the manufacturer that assumes responsibility for the safety, purity, and potency of the biological product, and compliance with applicable product and establishment standards (including compliance by any contract manufacturers). Contract facilities for biological products also are subject to FDA inspection and must register with FDA in accordance with FDA's drug registration and listing provisions.

Regulations enforced by U.S. Customs and Borders Protection generally require that articles of foreign origin (or their containers) are marked with their country of origin at the time of importation into the U.S. Manufacturers seeking to comply with U.S. Customs requirements may include this information on product or carton labeling if their product does not fall

within an exception, but this U.S. Customs requirement does not supersede FDA's requirement to list the name, address, and license number of the manufacturer on the package label and container label.

23. I appreciate the agencies focus on assimilating the purple book, but some have suggested that physicians and pharmacists will continue to utilize the product labeling as they have been accustomed to do. Do you think that the purple book is sufficient for providing the necessary safety information to providers? What is the harm in providing more information to providers about the characteristics of the product in the label?

Healthcare practitioners should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients. The Purple Book is not intended to be a resource for this information. FDA created the "Purple Book" on its own initiative to provide a convenient source of information regarding licensed biological products with reference product exclusivity, or biosimilarity or interchangeability evaluations.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products.* As described in that guidance, FDA recommends that biosimilar product labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The guidance further recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product.

To determine which indications have been approved for a biosimilar product, health care professionals are advised to review the labeling – prescribing information – of the biosimilar product.

24. In 2012, FDA issued a Draft Guidance[7] stating that the labeling of a proposed biosimilar product should clearly state that the product is approved as a biosimilar for a given indication, and whether the product has been determined to be interchangeable. In the Final Guidance issued in April, the Agency removed these statements. Can you please comment on why the Agency removed these statements from the Final Guidance? Does the Agency disagree with physicians that believe these two pieces of information to be material to prescribers?

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients. FDA's draft guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did

[7] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf)

not address labeling issues in its final guidance[8] because prior to finalizing this guidance, FDA announced that it expected to issue a draft guidance on labeling for biosimilar products.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. The draft guidance also recommends a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

25. The complexity and uniqueness of each biologic medicine require that FDA ensure that all biologics and biosimilars are thoroughly tested and meet the highest safety standards. If a child is to be given a biosimilar drug for pediatric arthritis, or pediatric inflammatory bowel disease, shouldn't their parent have the peace of mind of knowing that that biosimilar has undergone clinical testing for those specific conditions?

Approval of a biosimilar product is based on review of evidence that may include structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates that the product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency. FDA intends to use a totality-of-the-evidence approach to evaluate all available data and information submitted in support of a determination of biosimilarity of the proposed product. The type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis.

26. FDA recently released its proposed guidance on the non-proprietary naming of biosimilars. In it you specifically noted that you were not addressing future interchangeable biosimilars at this time, and asked for feedback on how to approach those products. Just a few months earlier in July, however, CMS proposed reimbursement policies for biosimilars entering the market without making such a distinction about interchangeable biosimilars. Is FDA communicating with CMS on where the regulatory pathway is on interchangeables? Do you think CMS should be addressing reimbursement for interchangeable products before your agency has developed the approval pathway?

Though FDA does not have a role in CMS coding decisions, in conjunction with the final rule on the Medicare Physician Fee Schedule for 2016, CMS and FDA developed and

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[8] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

implemented an approach to use manufacturer-specific modifiers to facilitate pharmacovigilance for biological products that share a billing code.

27. In addition to the regulatory approval requirements necessary for manufacturers to invest in the development of biosimilars, the other major variable is government reimbursement for biosimilars. In its recently proposed rule on biosimilars reimbursement, CMS left a number of questions unanswered, questions which are closely linked to the progress FDA is making on a number of its guidances. Is FDA communicating with CMS on these issues?

As stated above, FDA does not have a role in CMS reimbursement decisions. We are working together on pharmacovigilance.

28. Under Section 7002(e)(2) of the Biological Price and Innovation Competition Act, biological products that have been approved under an NDA under Section 505 of the Federal Food, Drug, and Cosmetic Act will be transitioned into a BLA under Section 351 of the Public Health Service Act by March 23, 2020. How does the FDA plan to address implementation of these transition provisions?

The BPCI Act changed the statutory authority under which certain protein products will be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)." The BPCI Act requires that a marketing application for a "biological product" must be submitted under section 351 of the PHS Act; this requirement is subject to certain exceptions during a 10-year transition period ending on March 23, 2020 (see section 7002(e)(1)-(3) and (e)(5) of the BPCI Act). On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4) of the BPCI Act). On March 11, 2016, FDA issued a draft guidance document on *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009.*

29. What is the FDA's stance on using post marketing data from countries like India for approval of biosimilars in the US?

In order for a product to be licensed as a biosimilar in the U.S., the data and information submitted to FDA must demonstrate that the proposed product is biosimilar to a U.S.-licensed reference product. If the product proposed for licensure in the US is already approved outside the U.S., postmarket data may be submitted to provide additional data to support the safety of the proposed biosimilar product. The relevance of the data would be considered during the review of the marketing application. However, postmarket data alone cannot provide adequate information to demonstrate that the proposed product is biosimilar to the U.S.-licensed reference product.

Information derived from postmarket data could provide some reassurance about adverse events. However, the quality of the information is highly dependent on the accuracy and reliability of the data collected.

30. The BPCIA includes a series of disclosure and patent exchange provisions that are often referred to collectively as the "patent dance." The goal of the patent dance is to compel the branded company and biosimilar applicant to identify only those patents that are relevant for purposes of litigation. However, in July, the Court of Appeals for the Federal Circuit ruled that the patent dance is optional.

FDA's Orange Book, which covers small molecule drugs, includes a listing of all relevant patents, while the Purple Book, which covers biologics, does not.

31. Does the FDA have the authority, on its own accord, to require that sponsors list all of the patents covering their biological products in the Purple Book?

The "Orange Book" is the "list" required by section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act, but no similar statutory requirement appears in the BPCI Act. FDA created the "Purple Book" to provide a convenient source of information regarding licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations.

Section 351(l) of the PHS Act describes procedures for information exchanges and the resolution of certain patent disputes between a biosimilar applicant and the reference product sponsor. These procedures are parallel to, but separate from, the FDA review process. The BPCI Act generally does not describe any FDA involvement in monitoring or enforcing the patent information exchange described in section 351(l) of the PHS Act, and does not require FDA to publish any patent-related information other than the notice of a complaint served to a 351(k) applicant in an action for patent infringement under section 351(l) of the PHS Act (see section 351(l)(6)(C)(ii) of the PHS Act).

32. I understand that FDA does not involve itself in disputes involving pharmaceutical patents; however, is there any reason why FDA would oppose the mere listing of patents in the Purple Book?

The Biologics Price Competition and Innovation Act of 2009 generally does not describe any FDA involvement in monitoring or enforcing the patent information exchange described in section 351(l) of the Public Health Service Act (PHS Act), and does not require FDA to publish any patent-related information other than the notice of a complaint served to a 351(k) applicant in an action for patent infringement under section 351(l) of the PHS Act (see section 351(l)(6)(C)(ii) of the PHS Act).

We note that even FDA's ministerial role in administering the patent listing provisions of the Hatch-Waxman Amendments and ensuring compliance with the patent certification requirements of the FD&C Act has been subject to challenge, and has embroiled the Agency in litigation. Any similar involvement in the context of the PHS Act could be expected to be resource intensive for FDA.

33. Is the FDA concerned about the threat of improperly listed patents? As part of Medicare Modernization Act of 2003, Congress gave generic applicants the ability to challenge the listing of a patent in the Orange Book by filing a counterclaim against the branded company in response to an infringement suit. [FFDCA §505(c)(3)(D)

(ii)(I)]. Would FDA have any issues with Congress implementing a similar approach with respect to the Purple Book?

Section 351(l) of the PHS Act describes procedures for information exchanges and the resolution of certain patent disputes between a biosimilar applicant and the reference product sponsor. These procedures are parallel to, but separate from, the FDA review process, and differ from the patent listing and patent certification requirements of the FD&C Act. The BPCI Act generally does not describe any FDA involvement in monitoring or enforcing the patent information exchange described in section 351(l) of the PHS Act, and does not require FDA to publish any patent-related information other than the notice of a complaint served to a 351(k) applicant in an action for patent infringement under section 351(l) of the PHS Act (see section 351(l)(6)(C)(ii) of the PHS Act).

We note that even FDA's ministerial role in administering the patent listing provisions of the Hatch Waxman Amendments and ensuring compliance with the patent certification requirements of the FD&C Act has been subject to challenge, and has embroiled the Agency in litigation. Any similar involvement in the context of the PHS Act could be expected to be resource intensive for FDA.

The statutory counterclaim provision in the FD&C Act has been considered by the U.S. Supreme Court in *Caraco Pharm. Labs. v. Novo Nordisk A/S* (2012). Justice Sotomayor noted in a concurring opinion: "the counterclaim cannot restore the smooth working of a statutory scheme thrown off kilter by an overly broad use code. At best, it permits the generic manufacturer to do what the scheme contemplates it should do—file an ANDA with a section viii statement—but only after expensive and time-consuming litigation" 132 S.Ct. 1670 at 1689.

The Honorable Michael C. Burgess

1. **In accordance with the transition requirements of the BPCIA, certain biological products that were originally approved under Section 505 of the FDC Act, like insulin and human growth hormone, will be deemed approved under Section 351 of the PHS Act. There are a number of unanswered questions with respect to what it means to be a product that is deemed licensed under the PHS Act, such as those related to exclusivity (including pediatric exclusivity), non-proprietary naming, A ratings and interchangeability, and scientific standards. Does FDA intend to address these questions in its forthcoming guidance document and how likely is it that the Agency will release such a guidance this year?**

On March 11, 2016, FDA released a draft guidance for industry on *Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).* This draft guidance describes FDA's approach to implementation of the statutory provision under which a marketing application for a biological product approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) on or before March 23, 2020, will be deemed to be a license for the biological product (i.e., an approved biologics license application (BLA)) under the Public Health Service Act (PHS Act) on March 23, 2020.

Although the majority of therapeutic biological products have been licensed under the PHS Act, some protein products (e.g., insulin and insulin analogs, human growth hormone, pancreatic enzymes, follitropin products) historically have been approved under the FD&C Act. The BPCI Act changed the statutory authority under which these protein products will be regulated by amending the statutory definition of a "biological product" in the PHS Act to include a "protein (except any chemically synthesized polypeptide)."

The BPCI Act describes requirements for submission of an application for a "biological product" during a 10-year transition period ending on March 23, 2020 (ten years after the date of enactment). On March 23, 2020, an approved marketing application for a biological product under section 505 of the FD&C Act will be deemed to be a license for the biological product under section 351 of the PHS Act. The draft guidance describes FDA's interpretation of this statutory provision, and explains that FDA will not approve any pending or tentatively approved application for a biological product under the FD&C Act after March 23, 2020. The draft guidance also provides recommendations to sponsors of proposed biological products intended for submission in a new drug application (NDA) (including a 505(b)(2) application) that may not receive final approval under the FD&C Act by March 23, 2020, to facilitate alignment of product development plans with FDA's interpretation of the transition provisions of the BPCI Act.

2. **For the first biosimilar approved, FDA did not require the label to identify the product as a biosimilar or to delineate the indications for which clinical data was generated. This decision seems to contradict FDA's past statements and guidance on this issue. What was the agency's rationale for omitting this important information?**

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

FDA's draft guidance on "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did not address labeling issues in its final guidance[9] because prior to finalizing this guidance, FDA announced that it would issue a draft guidance on labeling for biosimilar products. The public will be provided with an opportunity to comment on the draft guidance on labeling when it is published.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. The draft guidance also recommends a footnote to this statement explaining that, "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and

[9] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

that there are no clinically meaningful differences between the biosimilar product and the reference product."

3. **The first biosimilar label did not include any information about the different types of studies the company conducted or clinical data that was submitted. This type of scientific information is extremely important. Could the sponsor proactively provide this information to doctors and payers or would such activity be considered off-label promotion? Why or why not?**

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, it is FDA's view that biosimilar product labeling should generally not include data from a clinical study of a proposed biosimilar because such data are not likely to be relevant to a health care practitioner's considerations regarding the safe and effective use of the biosimilar product and may potentially cause confusion, resulting in an inaccurate understanding of the risk-benefit profile of the product.

FDA posts on its Web site certain documents generated by FDA related to its review of a 351(k) application, as appropriate. For products regulated by CDER, please see Drugs@FDA (*http://www.fda.gov/drugsatfda*). For products regulated by CBER, please see the CBER Freedom of Information Office Electronic Reading Room (*http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm129132.htm*).

Sponsors may proactively make truthful and non-misleading communications to doctors and payers that present clinical study data supporting FDA's determination of biosimilarity, for the approved application, that are not explicitly described in FDA-approved labeling. Please note that the truthful and non-misleading nature of such communications involves a fact-specific determination that would take into account such factors as the actual presentation, the type of clinical data (i.e., pharmacokinetics, pharmacodynamics, safety, or efficacy), the quality of the data, and the accuracy of any communications based upon this data, including the need to disclose material information. For example, presentations of data used to support a finding of biosimilarity but not interchangeability should not state or suggest that the studies demonstrated interchangeability between the biosimilar and reference product. Similarly, sponsors should not represent that studies used to support a finding of biosimilarity independently demonstrate the efficacy of the biosimilar, where the study was not designed to make such a determination.

4. **Healthcare providers have indicated that they want to know, when prescribing biosimilars, which indications were studied clinically and which were not. How do you plan to make sure providers have adequate information to feel comfortable prescribing biosimilars?**

FDA does not intend to differentiate between indications that were directly studied and those supported through extrapolation in product labeling. FDA undertakes a rigorous and

thorough evaluation to ensure that a biosimilar product meets the Agency's standard for approval. When FDA approves a biosimilar product, it has determined the product meets the Agency's standard for approval for all indications for which the biosimilar product is approved, including any approved indications that were supported by extrapolation. The biosimilar also has been demonstrated to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency, including for any indications that were supported by extrapolation.

FDA has issued final guidance outlining the issues that an applicant should consider when providing a scientific justification for extrapolating clinical data sufficient to demonstrate safety and effectiveness in one condition of use to support a determination of biosimilarity in one or more additional conditions of use for which licensure is sought.

FDA posts on its web site certain documents generated by FDA related to its review of a 351(k) application, as appropriate. For products regulated by CDER, please see Drugs@FDA (*http://www.fda.gov/drugsatfda*). For products regulated by CBER, please see the CBER Freedom of Information Office Electronic Reading Room (*http://www.fda.gov /AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm129132.htm*).

To determine which indications have been approved for a biosimilar product, health care professionals are advised to review the labeling – prescribing information – of the biosimilar product.

In addition, FDA has a multi-phase plan for communicating with stakeholders about biosimilar products. The first phase of communication is to lay a solid foundation with basic definitions and descriptions about biosimilar products that health care professionals and consumers can easily understand and adopt.

Concurrent with the approval of Zarxio, the first biosimilar product in the United States, FDA updated its website to provide more information about biosimilar products, including pages specifically for consumer[10] and health care professional[11] audiences. The content includes definitions of biosimilar products and interchangeable products, information on how health care professionals can prescribe these products, and the differences between biosimilar products and generic drugs.

FDA also released a Consumer Update[12] that outlined the basic concepts of biosimilar products.

FDA provided notification about the updated website and Consumer Update to many stakeholder and health care professional organizations and encouraged dissemination to their members and patients. FDA plans to communicate information in various formats to

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http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm

[11] *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm*

[12] *http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm*

consumers and health care providers as more biosimilar products are approved and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability.

Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to maximize health care provider and consumer confidence in this new category of products.

5. **If FDA adopts the distinguishable non-proprietary names for biologics unique to the license holder, what will happen when companies acquire or divest products?**

With the publication of our draft guidance, *Nonproprietary Naming of Biological Products*, FDA requested comment on whether the format of the suffix should be unique to each product or shared by those products made by a single license holder, whether or not the suffix should be devoid of meaning, and questions related to the naming of interchangeable products. FDA will carefully consider all comments that have been submitted to the public docket.

6. **In 2010 and 2012, the agency characterized interchangeability as a stringent standard, and as a higher standard than biosimilarity. However, more recently, FDA has used different language calling interchangeability simply an "additional" showing. What led to this change in FDA's position?**

The BPCI Act defines interchangeability to mean that the biological product has been shown to meet the statutory standards for interchangeability and may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The BPCI Act provides that FDA shall determine a proposed biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application is sufficient to show that (1) the biological product is biosimilar to the FDA-approved reference product, (2) the biological product can be expected to produce the same clinical result as the reference product in any given patient, and (3) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

FDA intends to issue draft guidance in the near future on *Considerations in Demonstrating Interchangeability With a Reference Product*.

7. **It is critical that FDA have clear review standards and processes in place to protect patient safety and ensure efficacy of biosimilar medicines prior to making decisions about these applications. It is also vital that the process used to develop these standards is transparent so that patients and the public have a full and fair opportunity to review and comment upon these standards before they are finally adopted. On a regular and ongoing basis, what specifically will FDA do to obtain**

input from patients, providers, and industry experts in biosimilar policy discussions? Will upcoming guidance on labeling, interchangeability, and other key issues come in draft form so these groups have an opportunity to review and comment on them before they become final?

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products* and expects to issue the following draft guidances in 2016 as reflected on the CDER Guidance Agenda: *Considerations in Demonstrating Interchangeability With a Reference Product*; and *Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity*. FDA will follow its good guidance practices for finalizing these draft guidance documents, which includes providing an opportunity for public comment before they are finalized.

8. **At the Senate HELP Committee hearing on biosimilars on September 17, 2015, Dr. Woodcock stated that FDA has a multi-year plan to educate patients about biosimilars. Was this developed in consultation with patient groups? Will FDA commit to working with patient groups to review this plan and make any necessary modifications?**

Elements of the communication plan are described above in the response to Question 4. In addition, FDA's Office of Health and Constituent Affairs has held two listening sessions, one with patient advocacy organizations and one with prescribers to understand their perspectives about biosimilars.

Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to maximize health care provider and consumer confidence in this new category of products.

9. **Factors, such as cost or state pharmacy laws, may force patients to switch from a biologic medicine to a biosimilar. How is FDA factoring this in to patient safety standards when approving biosimilars, labeling, and interchangeability?**

FDA considers the safety of patients who are taking any medical product to be of the utmost importance. We undertake a rigorous and thorough evaluation to ensure that a biosimilar product meets the statutory standard for approval. The final guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, states that "depending on the clinical experience of the reference product and proposed products (taking into consideration the conditions of use and patient population), a sponsor may need to evaluate a subset of patients to provide a substantive descriptive assessment of whether a single cross-over from the reference product to the proposed biosimilar would result in a major risk in terms of hypersensitivity, immunogenicity or other reactions." The guidance continues that "[d]ifferences in immune responses between a proposed product and the reference product in the absence of observed clinical sequelae may be of concern and may warrant further evaluation (e.g., extended period of follow-up evaluation)." FDA intends to use a risk-based totality-of-the-evidence approach to evaluate all available data and information submitted, including this assessment, in support of a determination of biosimilarity of the proposed product.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. As reflected on the CDER Guidance Agenda, FDA expects to issue draft guidance on interchangeability in 2016 (*Considerations in Demonstrating Interchangeability With a Reference Product*).

The Honorable Gus Bilirakis

1. **Dr. Woodcock, FDA will be transitioning a number of biologics that were previously approved as drugs into the biologics regulatory regime by 2020. How does the agency plan on doing so as seamlessly as possible?**

On March 11, 2016, FDA released a draft guidance for industry on *Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)*. This draft guidance describes FDA's approach to implementation of the statutory provision under which a marketing application for a biological product approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) on or before March 23, 2020, will be deemed to be a license for the biological product (i.e., an approved biologics license application (BLA)) under the Public Health Service Act (PHS Act) on March 23, 2020.

Although the majority of therapeutic biological products have been licensed under the PHS Act, some protein products (e.g., insulin and insulin analogs, human growth hormone, pancreatic enzymes, follitropin products) historically have been approved under the FD&C Act. The BPCI Act changed the statutory authority under which these protein products will be regulated by amending the statutory definition of a "biological product" in the PHS Act to include a "protein (except any chemically synthesized polypeptide)."

The BPCI Act describes requirements for submission of an application for a "biological product" during a 10-year transition period ending on March 23, 2020 (ten years after the date of enactment). On March 23, 2020, an approved marketing application for a biological product under section 505 of the FD&C Act will be deemed to be a license for the biological product under section 351 of the PHS Act. The draft guidance describes FDA's interpretation of this statutory provision, and explains that FDA will not approve any pending or tentatively approved application for a biological product under the FD&C Act after March 23, 2020. The draft guidance also provides recommendations to sponsors of proposed biological products intended for submission in a new drug application (NDA) (including a 505(b)(2) application) that may not receive final approval under the FD&C Act by March 23, 2020, to facilitate alignment of product development plans with FDA's interpretation of the transition provisions of the BPCI Act.

The Honorable Renee Ellmers

1. **During the February 4, 2015 Energy and Commerce Health Subcommittee hearing titled, "Examining Implementation of the Biologics Price Competition and**

Innovation Act" I stated to you that a letter to Acting Commissioner Ostroff from the House Doctor's Caucus dated December 21, 2015 had not received a response. I requested that it be submitted for the hearing record. If you could please provide the committee and the members who signed that letter a status on the response to it, I would greatly appreciate it. Again, this is a very important issue that has been raised to the House Doctors Caucus attention by physicians and patients.

FDA provided a response to you and your colleagues on March 11, 2016, which is provided for reference (see Enclosure B).

2. **You stated at the Senate hearing last year that provider and patient confidence in biosimilars is critical to the success of the program and that the agency needs to ensure that the scientific framework is "bulletproof." Recently, twelve members of the House Doctor's Caucus – including myself – sent a letter to Acting Commissioner Ostroff with concerns regarding a lack of transparency on the label for the first biosimilar approved last year as well as the FDA's suggestion that physicians reference the Purple Book regarding interchangability of biosimilars. Mr. Chairman, I respectfully ask that this letter be entered into the record. Dr. Woodcock, I along with the other members of the Doctor's Caucus who signed this letter would appreciate a timely response. In the interim could you speak about the FDA's actions prior to and during the consideration of the approval of the first biosimilar product to ensure physician confidence in these products?**

FDA has a multi-phase plan for communicating with stakeholders about biosimilar products. The first phase of communication is to lay a solid foundation with basic definitions and descriptions about biosimilar products that health care professionals and consumers can easily understand and adopt.

Concurrent with the approval of Zarxio, the first biosimilar product licensed in the United States, FDA updated its website to provide more information about biosimilar products, including pages specifically for consumer and health care professional audiences. The content includes definitions of biosimilar products and interchangeable products, information on how health care professionals can prescribe these products, and the differences between biosimilar products and generic drugs.

FDA also released a Consumer Update that outlined the basic concepts of biosimilar products.

FDA provided notification about the updated website and Consumer Update to many stakeholder and health care professional organizations and encouraged dissemination to their members and patients. FDA plans to communicate information in various formats to consumers and health care providers as more biosimilar products are approved and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability.

Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to maximize health care provider and consumer confidence in this new category of products.

3. **This first approved biosimilar was given a four digit suffix abbreviating the company's name in order to differentiate it from the reference product. The draft guidance, while requesting additional feedback on the matter, proposes a different approach that would assign a random suffix that is "devoid of meaning." Can you walk me through FDA's current thinking on this and the factors you are going to consider before making your final decision?**

In August 2015, FDA published a draft guidance entitled *Nonproprietary Naming of Biological Products*. As described in that guidance, FDA recommends that both previously licensed and newly licensed biological products should have nonproprietary names (also called a proper name) that include a core drug substance name and, in order to better identify each product, an FDA-designated suffix that is devoid of meaning. However, the Agency requested comment on the benefits and challenges of designating a nonproprietary name with a meaningful suffix which is derived from the name of the license holder. FDA is carefully considering the many comments we received on this and other aspects of the proposed naming convention.

4. **The FDA has done an admirable job in uncovering problems with Indian manufacturing of generic medicines. However, numerous examples still exist of Indian companies with dubious production records continuing to sell products in the US. Given that biosmiliars are far harder to produce than small molecule generics, what extra safeguards, such as demanding spotless export records for three years, will FDA put in place if Indian biosimilars are ever approved for sale in US?"**

All registered drug manufacturing facilities are subject to inspection, with inspection frequency determined on the basis of risk to patients. FDA's employs a highly trained inspectorate, which is skilled in uncovering failures in good manufacturing practice. Whenever FDA investigators find product quality issues that potentially implicate drug safety and efficacy, the Agency takes appropriate action, which could include issuing a warning letter or import alert, or taking other enforcement action. All FDA-approved drugs delivered to patients in the United States are subject to the same high standards, regardless of country of origin.

<u>The Honorable Susan Brooks</u>

1. **Dr. Woodcock, if a biosimilar is not initially determined to be interchangeable at the time of approval, could it eventually achieve such status and, if so, can you explain the logistical and communications challenges such a situation would present and how FDA would deal with them?**

Following approval of a product as a biosimilar, the applicant could submit a supplemental application containing additional data and information to support a demonstration of interchangeability to FDA for review. . FDA plans to communicate information in various formats to consumers and health care providers as more biosimilar products are approved and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability.

2. **The patent provisions contained within BPCIA were carefully crafted after much debate among all stakeholders. They create a two-round scheme for resolution of potential patent disputes. The first opportunity for patent litigation is designed to provide resolution of at least some relevant patents far in advance of a biosimilar approval. Are you concerned that even though you may have approved a product, it may still not reach patients because of pending patent litigation that must be resolved?**

    a. **If not, why are you not concerned given that the goal is to get these new medicines to patients?**

    b. **If yes, is there anything that Congress should do to help provide a more certain process to ensure patent disputes are resolved in a timely manner?**

    Section 351(l) of the Public Health Service Act (PHS Act) describes procedures for information exchanges and the resolution of certain patent disputes between a biosimilar applicant and the reference product sponsor. These procedures are parallel to, but separate from, the FDA review process, and differ from the patent listing and patent certification requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Biologics Price Competition and Innovation Act of 2009 generally does not describe any FDA involvement in monitoring or enforcing the patent information exchange described in section 351(l) of the PHS Act, and does not require FDA to publish any patent-related information other than the notice of a complaint served to a 351(k) applicant in an action for patent infringement under section 351(l) of the PHS Act (see section 351(l)(6)(C)(ii) of the PHS Act).

    We note that even FDA's ministerial role in administering the patent listing provisions of the Hatch-Waxman Amendments and ensuring compliance with the patent certification requirements of the FD&C Act has been subject to challenge, and has embroiled the Agency in litigation. Any similar involvement in the context of the PHS Act could be expected to be resource-intensive for FDA.

<u>The Honorable Chris Collins</u>

FDA has stated a need to identify biological products *clearly*, in order to differentiate among biological products that have not been determined to be interchangeable. The only approved biosimilar received a nonproprietary name followed by a 4-letter code signifying

the company responsible for marketing the medication. However, we have heard from constituents that are biologics prescribers that a suffix must also be memorable.

1. **Will the FDA's next approval of a biosimilar provide clear guidance on biosimilar naming? Can you share any insight on how FDA may proceed with regard to the four-letter suffix and differentiating products?**

In August 2015, FDA issued a draft guidance entitled *Nonproprietary Naming of Biological Products*. As described in that guidance, FDA recommends that both previously licensed and newly licensed biological products should have nonproprietary names (also called a proper name) that include a core drug substance name and, in order to better identify each product, an FDA-designated suffix that is devoid of meaning. However, the Agency requested comment on the benefits and challenges of designating a nonproprietary name with a meaningful suffix which is derived from the name of the license holder. FDA is carefully considering the many comments we received on this and other aspects of the proposed naming convention.

Physicians want the most accurate information possible so that they can make decisions in the best interest of their patients, undoubtedly. Physicians are responsible for prescribing the biosimilar and treating adverse side effects that may result.

2. **How does the agency plan to increase transparency in a biosimilar's prescribing information, whereby the prescription drug labeling information will clearly indicate whether the information is based on the biosimilar product or on the reference biologic?**

Health care professionals should have product labeling that includes the essential scientific information about the safety and efficacy profile of a product necessary to make informed prescribing decisions for their patients.

FDA's draft guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* described a labeling approach that would include a statement regarding biosimilarity or interchangeability. However, FDA did not address labeling issues in its final guidance[13] because prior to finalizing this guidance, FDA announced it would issue a draft guidance on labeling for biosimilar products.

On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. Additionally, FDA recommends that biosimilar labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. FDA further recommends that when clinical studies or data derived from the studies with the reference product are described in biosimilar product labeling, the reference product's proper name

[13] *Scientific Consideration in Demonstrating Biosimilarity to a Reference Product*, available at *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.*

should be used. Such usage will indicate when data described in the biosimilar product's labeling is derived from studies of the reference product rather than the biosimilar product.

3. **What is your agency doing to ensure safety of a biosimilar drug for more than one indication? Will clinical testing be required for each indication before it can be used to treat patients for that indication? For example, if a reference biological medication is approved for five different indications, it has been specifically tested in different patient groups with each of the five different medical conditions. Will this be the same for biosimilars?**

FDA undertakes a rigorous and thorough evaluation to ensure that a biosimilar product meets the statutory standard for approval. When FDA approves a biosimilar product, it has determined the product meets the statutory standard for approval and has been demonstrated to have no clinically meaningful differences from the reference product in terms of safety, purity, and potency, including any indications that were supported by extrapolation. Approval of a biosimilar product is based on review of evidence that may include structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates that the product is highly similar to the reference product and that there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency.

FDA has issued final guidance outlining the issues that an applicant should consider when providing a scientific justification for extrapolating clinical data sufficient to demonstrate safety and effectiveness in one condition of use to support a determination of biosimilarity in one or more additional conditions of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- the mechanism(s) of action in each condition of use for which licensure is sought; this may include:
  - the target/receptor(s) for each relevant activity/function of the product;
  - the binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
  - the relationships between product structure and target/receptor interactions;
  - the location and expression of the target/receptor(s);
- the PK and bio-distribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- the immunogenicity of the product in different patient populations;
- differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to "off-target" activities); and
- any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Differences between tested and extrapolated conditions of use with respect to the factors described above do not necessarily preclude extrapolation, but differences need to be addressed. The applicant should ensure that the totality of the evidence submitted, including scientific justification for extrapolation, supports its approach.

4. **Europe has preceded the U.S. in approvals of biosimilars. Will FDA use data from those approvals, and specifically post-market data, to inform FDA's decisions on indication approvals?**

Under section 351(k) of the PHS Act, an applicant may include any additional information in support of the application, including publicly available information with respect to the reference product or another biological product. FDA intends to use a risk-based, totality-of-the-evidence approach to evaluate all available data and information submitted in support of a proposed biosimilar application, including such information related to another biological product such as those that are marketed in Europe.

The Honorable Lois Capps

Dr. Woodcock, we have already heard that one main area that needs to be clarified in order to set up a robust biosimilars market is to gain clarity on how these products should be labeled. As a nurse, I understand the importance of an accurate and useful labeling system for health care providers. But it is also an important tool for patients, so that they understand what they are taking and can be active participants in their own care. Clearly, all the stakeholders in this conversation are eager for clear guidance from FDA on how these life-saving products should be labeled.

1. **Dr. Woodcock, can you tell us more about the steps FDA plans to take to ensure that these labels are useful and usable for not only providers and payers, but for patients as well? How is their experience factoring into FDA's thinking on this matter?**

Healthcare professionals should have product labeling that includes the essential scientific information necessary to make informed prescribing decisions for their patients. Health care professionals are advised to review the labeling (prescribing information) of the biosimilar product to determine which conditions of use and routes of administration the biosimilar was approved for. A biosimilar product can be approved by FDA for some or all of the same uses as the FDA-approved reference product that the biosimilar was compared to, and prescribed by a health care professional as appropriate. On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in that guidance, FDA recommends inclusion of a statement in the biosimilar product's Highlights of Prescribing Information that the product is biosimilar to the reference product. FDA further recommends that biosimilar labeling incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications. The public has been provided with an opportunity to comment on this draft guidance.

Dr. Woodcock, as you noted in your testimony, confidence from patients and health care professionals is critical to the success of the biosimilar market. I believe this confidence in

part will come through a better understanding of biosimilars by patients and health care professionals. You have indicated that FDA will take a multi-phase approach to education and outreach, including message development, training programs, and partnerships with outside organizations.

2. **I appreciate that FDA is taking a multi-pronged approach to education and outreach efforts. Can you please discuss further the multi-phase education and outreach plan FDA has developed, as well as what resources FDA has, or may need, to fully implement this plan? As you know, the fifth authorization of PDUFA and the House passed Cures has emphasized the benefit for including the patient perspective in the drug development process. How will FDA incorporate the patient perspective as a part of your planning and outreach efforts related to biosimilars?**

FDA is currently engaging stakeholders to learn about their concerns and potential information gaps. FDA's Office of Health and Constituent Affairs has held two listening sessions, one with patient advocacy organizations and one with prescribers to understand their perspectives about biosimilars. FDA is also conducting qualitative research with physicians, nurse practitioners and pharmacists to learn more about their perspectives on biosimilars, where their trusted sources of information come from and what kinds of information they need. Additionally, we have developed a CME (continuing medical education) course for prescribers about biosimilars that was released to the public on February 18, 2016. In the coming months, the FDA plans to develop communication materials to educate consumers and health care professionals. These will be posted on the FDA biosimilar web pages and distributed to stakeholders through email and conferences.