

**BIOSIMILAR IMPLEMENTATION: A PROGRESS
REPORT FROM FDA**

HEARING

BEFORE

THE SUBCOMMITTEE ON PRIMARY HEALTH AND
RETIREMENT SECURITY
OF THE
COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED FOURTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING BIOSIMILAR IMPLEMENTATION, FOCUSING ON A PROGRESS
REPORT FROM FDA

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SEPTEMBER 17, 2015
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BIOSIMILAR IMPLEMENTATION: A PROGRESS REPORT FROM FDA

THURSDAY, SEPTEMBER 17, 2015

U.S. SENATE,
SUBCOMMITTEE ON PRIMARY HEALTH AND RETIREMENT
SECURITY,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Bill Cassidy, presiding.

Present: Senators Cassidy, Alexander, Murphy, Scott, Warren, Kirk, and Hatch.

OPENING STATEMENT OF SENATOR CASSIDY

Senator CASSIDY. The Committee on Health, Education, Labor, and Pension, Subcommittee on Primary Health and Retirement Security will please come to order.

This morning we have a hearing titled Biosimilar Implementation: A Progress Report from FDA. Ranking Member Murphy and I will each have an opening statement and then introduce our witness. After our witness' testimony, Senators will each have 5 minutes of questions.

First, I thank Chairman Alexander and Chairman Enzi for the opportunity to chair this hearing on the important issue of biosimilars, and Senator Murphy for joining as Ranking Member, and Dr. Woodcock in advance for her preparation and testimony.

Biologics are medicines derived from living cells, which makes them significantly more complex than the traditional medicines, which are sometimes called small molecules and are chemical compounds. The greater complexity of biologics makes them far more difficult and expensive to develop, manufacture, and to copy. Biosimilars, which are also called follow-ons, are biologics that copy so-called reference biologics and reference biologics are also called innovator drugs. Reference biologics are defined as the first biologic product released for a particular therapeutic effect.

Another key concept is interchangeability. If a biosimilar is so similar in effectiveness to the reference drug, the two could be swapped for each other. This is the highest bar for establishing similarity. Establishing biosimilarity, however, is the rub. While it can be certain that the effect of a small molecule or a traditional generic is identical to the original patented medicine, it has been thought that the complexity of biologics is such that one can never

be certain that the therapeutic effect of a biosimilar is identical to a reference biologic.

On the other hand, the complexity of biologics is such that one lot or batch of a reference product may not be identical to another lot of the same reference product. To put a point on it, there's a regulatory tension. FDA must ensure that biosimilars have a substantially similar safety profile and therapeutic efficacy as the innovator drug, but since a biosimilar is only similar and not exactly identical to the innovator drug the question is what evidence is required to prove biosimilarity and perhaps interchangeability.

The Biologics Price Competition and Innovation Act authorize the FDA to develop an approval pathway for biosimilar drugs.

While the regulatory incentive structure of the BPCIA roughly resembles that of the Hatch-Waxman structure for small molecules, a structure developed in part by our colleague on the committee Senator Hatch, there are significant differences. Because biologics are more expensive to produce and more difficult to receive patent protection, biologics received 12 years of data exclusivity instead of five. Because a biosimilar molecule can never be identical to the reference biologic molecule, or so it's thought, more data is required to demonstrate safety and efficacy to the FDA than a small molecule generic, which must only demonstrate bioequivalence. These are just a few of the differences.

Even though the BPCIA passed nearly 6 years ago and a biosimilar has already been approved and is now on the market, there is still uncertainty regarding how the FDA will implement the biosimilar approval pathway. In particular, the agency has still not provided final guidance on key issues of naming, labeling, interchangeability, and data extrapolation. We also don't know how these products will be reimbursed by CMS.

Our office has met with a number of stakeholders who requested clarity from the administration regarding these issues. Dr. Woodcock has graciously agreed to help provide such clarity. I will now ask Ranking Member Murphy for his opening statement. Senator Murphy.

OPENING STATEMENT OF SENATOR MURPHY

Senator MURPHY. Thank you very much, Mr. Chairman. Let me add my thanks to Senator Enzi, Senator Sanders, and the full committee for allowing us to serve as Chair and Ranking Member of this hearing.

I'd also like to thank Dr. Woodcock for testifying today giving us an update on the implementation of the biosimilar pathway.

Biologics have provided major advances in the treatment of cancer, rheumatologic disease, and other conditions. They also come at great costs to our healthcare system due to the expense of developing and manufacturing these drugs. For example, even though they account right now for less than 1 percent of prescriptions dispensed in the United States, expenditures on biologics amount to 28 percent of prescription drug spending. Both their use and their costs are forecast to grow sharply over the coming years. This increased cost is born by our healthcare system as a whole, but more specifically by patients as more and more insurance companies

place higher cost sharing burdens on biologics. I hope that we can talk about that today.

This underscores the need to build a robust biosimilar market. While we may never get close to the price reductions that are seen in the generic market, biosimilars will likely be 15 to 30 percent cheaper than the referenced biologic. These reductions will result in significant savings to the healthcare system and patients as the biosimilar market matures.

Biosimilars present so many interesting scientific and policy questions that we need to balance these as we look to promote access to these life changing drugs. Issues that are relatively easy when it comes to small molecule drugs, like naming, labeling, interchangeability, extrapolation, or reimbursement, are much more difficult due to the complex nature of biologics.

I commend Dr. Woodcock and the scientists at FDA for working through these challenging issues because I can understand the benefits of both sides of many of these arguments.

To that end, I was glad to see FDA finalize some of the guidances that were proposed in draft form in 2012 and released the new naming guidance last month, which I'm sure will be a topic of discussion today.

Providing the public the ability to comment on these difficult questions as the agency sets the "rules of the road" for the new pathway is critically important. Understandably, the industry needs to have some certainty on these outstanding questions as they think about investing hundreds of millions of dollars into biosimilar. Patient and provider groups they also need to have confidence in the end products as well.

We spent \$374 billion in 2004 on prescription drugs. That was a 13 percent increase over the prior year. There's a lot of reasons for that, but one of those is that there are less generics on the market than we would have liked. We need to grapple with this sort of strange world in which we live in today in which if you're a patient and you get provided a prescription you are likely going to get that prescription. Someone's going to pay for it. You're going to pay for it, but your insurance company is more likely. Patients have to fight like hell to get all sorts of other healthcare services: to get reimbursement for outpatient mental health or physical therapy or nutrition services.

We have a growing disparity between the amount of money that expended on pharmaceuticals and the amount of money that is spent on a lot of other very, very important therapies.

Senator Cassidy, thank you for allowing me to say a few words. I look forward to hearing from the witness.

Thank you. And now to introduce our witness, I'm delighted to welcome Dr. Woodcock as our only witness. Again, thank you for your time being here.

Dr. Woodcock is the Director of the Center for Drug Evaluation and Research, or abbreviated CDER, at the Food and Drug Administration. As of January 2015, Dr. Woodcock also assumed the role of Acting Director of CDER's newly formed Office of Pharmaceutical Quality.

Dr. Woodcock first joined the center in 1994. For 3 years she served as FDA's commissioner holding several positions including

deputy commissioner served FDA's commissioner holding these positions as well as deputy commissioner for operations and chief operating officer. Her responsibilities involved oversight of various aspects of scientific and medical regulatory operations.

Before joining the center, Dr. Woodcock served as the Director of the Office of Therapeutics Research and Review and Acting Deputy Director in FDA's Center for Biologic Evaluation and Research. She received her medical doctor degree from Northwestern Medical School and completed further training and held teaching appointments at Penn State University and UC San Francisco. She joined FDA in 1986.

Dr. Woodcock.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD

Dr. WOODCOCK. Thank you very much and good morning. I really thank all of you for holding this hearing today. It's a very important topic.

FDA and I personally have long supported the availability of a biosimilar pathway. In fact, I've been working on this since the late 1990s. This is very important to me. I've been involved in the development of biological therapeutics for about 30 years.

As a rheumatologist, which is an arthritis doctor, I have seen a transformation in the treatment of rheumatoid arthritis by these medicines. Due in large part to the biologic therapeutics, clinics full of wheelchairs are now a thing of the past in the rheumatology clinics. Instead of talking about joint replacements for these patients and ongoing care we talk about treating them to remission of disease: trying to make their disease go away.

I hear from my colleagues in rheumatology that these transformative medicines are still inaccessible to some Americans because of their costs.

Since the biosimilars pathways created by Congress in 2010, a lot of progress has been made. As the Chairman said, the first biosimilar was recently approved in the United States. Of course people are anxious to see more progress.

Our generics program, the small molecules that Senator Cassidy referred to, is now hugely successful with over 85 percent of dispensed prescriptions in the United States being generic drugs. This saves hundreds of billions of dollars to healthcare system. This success I have to stress did not happen overnight. It has been the work of many decades developing both maturity in the industry and gaining the confidence of the healthcare community to use generics this broadly.

Although the first biosimilar is now marketed, there are many legal, technical, and policy challenges ahead, and I look forward to discussing them as the subject of today's hearing. Nevertheless, I believe there is a bright future ahead for our biosimilars program and that it will produce the same access to important medicines that our current generics program is doing.

I'm happy to answer questions.

[The prepared statement of Dr. Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, M.D.

INTRODUCTION

Mr. Chairman and members of the subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss FDA's implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). FDA is supportive of and fully engaged with the development and approval of biosimilar and interchangeable biological products. Many of our most important drugs are biological products. Biological products are used to treat patients who have serious and life-threatening medical conditions including rheumatoid arthritis, diabetes, and cancer. It is important for the public health of the U.S. population to have access to safe, effective, and affordable biological products. Biosimilars can provide more treatment options for patients, and possibly lower treatment costs, enabling greater access for more patients.

To earn and sustain both physicians' and patients' confidence in biosimilar and interchangeable products, FDA must apply a scientifically rigorous review process and approval standard. Healthcare providers have consistently indicated the importance of assurance that biosimilars will have the same clinical performance as the originator, or reference product. FDA is committed to providing this assurance, and recognizes its importance to the uptake and acceptance of these products, and the future success of the biosimilars program.

BIOLOGICS PRICE COMPETITION AND INNOVATION ACT (BPCI ACT) AND BIOSIMILARS
USER FEE ACT (BSUFA): IMPORTANT ADDITIONS TO FDA STATUTORY AUTHORITY

As you know, the Affordable Care Act included the BPCI Act, which established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. With this new abbreviated approval pathway, a sponsor can get a biosimilar approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Biological products consist of large, complex molecules that are difficult to define and produce. This is in contrast to "small molecule" drugs that generally are produced through chemical processes, and can be replicated as "generic" drugs that are essentially exact copies. Unlike generic drugs, biosimilars must be highly similar to, not the same as, the reference product to which they are compared. A biosimilar can have certain allowable differences because it is made from living organisms, but it must demonstrate no clinically meaningful differences in terms of safety, purity and potency from its reference product. The complexity of biological products generally makes it more challenging to demonstrate biosimilarity, as compared to demonstrating sameness for a generic drug.

The abbreviated approval pathway permits a biosimilar biological product to rely on certain existing scientific knowledge about the safety and effectiveness of the reference product, saving the sponsor time and resources and thereby encouraging price competition and lower consumer healthcare costs. The ongoing and future impact of this relatively new law cannot be overstated. FDA's biosimilars program has sparked the development of a new segment of the biotechnology industry in the United States. The development of this new market segment should expand opportunities for technical innovation, job growth, and patient access to treatment.

The BPCI Act directed FDA to develop recommendations for a biosimilars user fee program for fiscal years 2013 through 2017. The first Biosimilar User Fee Act, or BsUFA, was enacted as part of the FDA Safety and Innovation Act (Public Law No. 112-144, enacted on July 9, 2012). BsUFA has allowed FDA to begin development of the infrastructure needed to support this new program. In addition, it has allowed the Agency to work toward devoting additional resources to meeting with companies regarding specific products in the pipeline to help streamline the drug development process leading to the approval of safe, effective, and possibly less expensive, biosimilar products for patients.

IMPLEMENTATION AND ACCOMPLISHMENTS

Probably the most exciting accomplishment since the enactment of the BPCI Act is FDA's approval of the first biosimilar in the United States. On March 6, 2015, FDA approved the first biosimilar, Zarxio (filgrastim-sndz), a biosimilar to Neupogen (filgrastim), a reference product licensed by FDA that is used to help stimulate growth of white blood cells in patients with cancer and help them fight infection.

FDA has worked hard to implement this new abbreviated licensure pathway. We established an internal cross-center working group, known as the Biosimilars Implementation Committee, to develop policies and procedures for implementation of the new law in a manner that best serves the public health. We created a multi-disciplinary committee known as the Biosimilars Review Committee, within CDER and the Center for Biologics Evaluation and Research (CBER), to provide central oversight and advice to review staff as they review and consider biosimilar development programs and related issues.

FDA has worked diligently to issue multiple guidances on biosimilars since enactment of the BPCI Act. Scientific guidance is of critical importance to lay the foundation for the development of biosimilar products. Although the BPCI Act does not require FDA to issue guidances before taking an approval action on a biosimilar application, we recognize the importance of guidances in helping to ensure successful implementation of this new pathway. These guidance documents provide transparency to industry, the healthcare community and other stakeholders with regard to FDA's scientific standards and approval criteria.

The necessary first step was to develop guidance regarding implementation of the BPCI Act and demonstrating biosimilarity. FDA published draft guidances in 2012 and published *final* guidances in April 2015 on the following topics:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.
- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product.
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.

We have also published the following *draft* guidances since 2012:

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.
- Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act.
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.
- Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009.
- Nonproprietary Naming of Biological Products.

FDA's most recent draft guidance on the Nonproprietary Naming of Biological Products describes FDA's current thinking on the appropriate naming convention to help ensure the safety of patients receiving biological products and maximize the success of biosimilar and interchangeable biological products. FDA believes that both reference products and biosimilars should have nonproprietary names (also called a proper name) that include a core drug substance name and, in order to facilitate safe use and pharmacovigilance, an FDA-designated suffix that is unique for each product. The agency is continuing to consider whether the nonproprietary name for an interchangeable product should include a unique suffix or share the same suffix as its reference product.

Along with this draft guidance, FDA issued a proposed rule that would designate nonproprietary names that contain a suffix for six previously licensed biological products. These products include four originator biological products that are reference products for an approved or publicly disclosed biosimilar application, a related biological product to one of these reference products, and a biosimilar product.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances and proposed rule noted above. Upcoming guidances are expected to include:

- Considerations in Demonstrating Interchangeability to a Reference Product.
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity.
- Labeling for Biosimilar Biological Products.

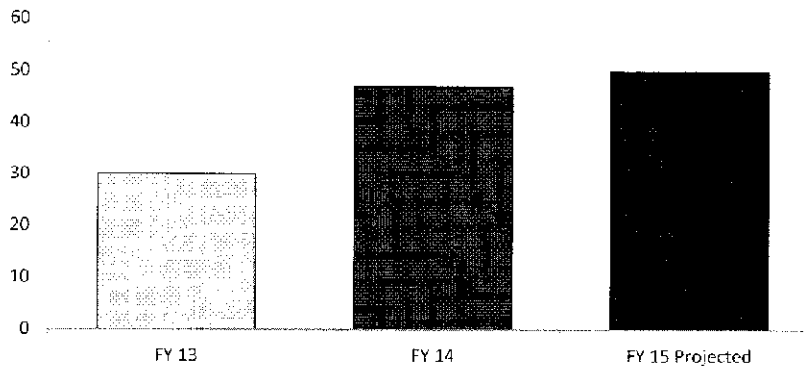
REVIEW PROGRAM

The biosimilar review program has continued to mature over time. As of July 31, 2015, 57 proposed biosimilar products to 16 different reference products were enrolled in the Biosimilar Product Development (BPD) Program. The BPD Program was created as a part of BsUFA to provide a mechanism and structure for the collection of development-phase user fees to support FDA's biosimilar review program activities. When a sponsor joins the BPD Program and pays the associated user fee for a specific product development program, that program is managed by FDA per

the BsUFA performance goals and procedures. The number of sponsors in the BPD Program is not absolutely reflective of the overall number of industry programs underway, as a sponsor may be in the early stages of interacting with FDA and not yet enrolled in the BPD Program. Sponsors of an additional 27 proposed biosimilar products have had a Biosimilar Initial Advisory meeting with FDA, but have not joined the BPD program to pursue the development of these products.

In engaging with sponsors regarding biosimilar development, CDER holds development-phase meetings and provides written advice for ongoing development programs. CDER continues to meet with sponsors interested in developing biosimilar products. The number of meeting requests increased 69 percent from the fiscal year 2013 level, from 32 to 54. The number of scheduled meetings also increased 57 percent during the second year of the biosimilar program, from 30 to 47. Based on the current and projected workload analysis, FDA expects continued modest growth in the number of meetings requested and scheduled through fiscal year 2015.

Number of Scheduled Meetings by Fiscal Year



Total number of scheduled meetings continue to grow each Fiscal Year. FY'15 projections calculated by doubling the total number of meetings scheduled through Q2 FY'15 (March 31, 2015).

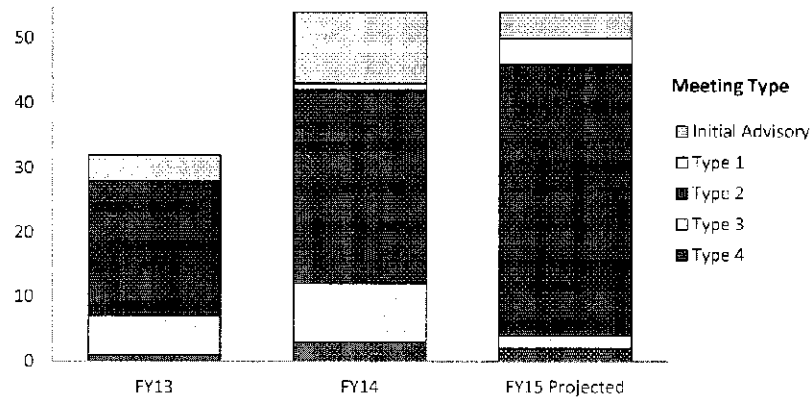
As biosimilar development programs mature, the type of interaction with FDA is changing. We have seen a shift in the types of meetings sponsors request and FDA grants. BsUFA established five meeting types specific to biosimilar development programs. Sponsors can choose the type of meeting or a combination of meetings to match development needs. Sponsors are increasingly requesting Biological Product Development (BPD) Type 2 meetings to discuss specific aspects of their development programs. This approach facilitates biosimilar product development by providing a process for iterative advice and clarity throughout the development stage.

The BsUFA program established five meeting types specific to biosimilar development programs:

- A Biosimilar Initial Advisory meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service (PHS) Act may be feasible for a particular product.
- A BPD Type 1 meeting is a meeting that is necessary for an otherwise stalled BPD program to proceed. Examples of a BPD Type 1 meeting include discussion of a clinical hold, a special protocol assessment meeting, discussion of an important safety issue, dispute resolution meetings, and discussion of a Complete Response.
- A BPD Type 2 meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing BPD program. This meeting type includes substantive review of summary data, but does not include review of full study reports.
- A BPD Type 3 meeting is an in-depth data review and advice meeting regarding an ongoing BPD program. This meeting type includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding the need for additional studies, including design and analysis. This meeting has no counterpart in the Prescription Drug User Fee Act (PDUFA) program and is unique to BsUFA to support an evaluation of residual uncertainty regarding the demonstration of biosimilarity and to support the concept of stepwise evidence development.

- A BPD Type 4 meeting is a meeting to discuss the format and content of a bio-similar biological product application or supplement to be submitted under section 351(k) of the PHS Act.

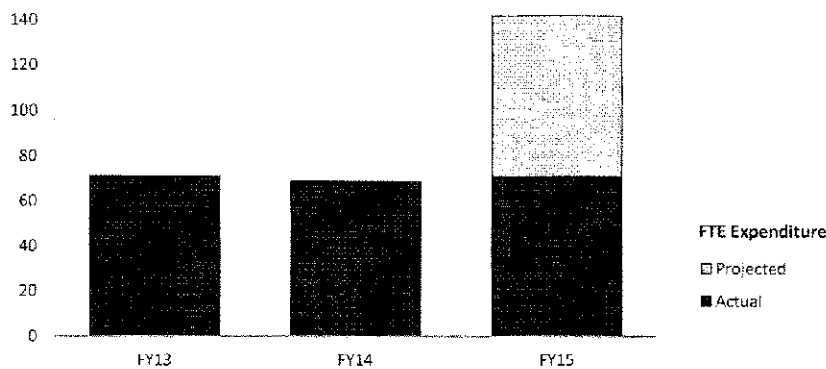
Scheduled Meetings by Type and Fiscal Year



The types of scheduled meetings shift with each fiscal year, with BPD Type 1 and Type 2 meetings becoming a larger portion of scheduled meetings in FY'15. FY'15 projections calculated by doubling the number of meetings scheduled by type, through the end of Q2 (March 31, 2015).

While we have made significant progress in implementing this new program, there is more work to do and, as with any new initiative, challenges to address. There are challenges relating to the BsUFA statutory requirement that FDA spend a certain level of BA funding in order to have the authority to collect and spend the user fee funds. FDA has taken steps to attempt to address this issue. FDA also is working to recruit additional staff and has continued to allocate increasing resources for this critical regulatory review program. FDA has continued to allocate increasing resources to the biosimilar review program. While the FTE expenditure in fiscal years 2013 and 2014 were relatively equal, the FTE expenditure in the first two quarters of fiscal year 2015 was equivalent to the total expenditures in the previous two fiscal years. FDA projects that the total FTE expenditure will be significantly greater in fiscal year 2015 than in previous fiscal years.

FTE Expenditure by Fiscal Year



Actual FTE expenditure based on calculation documented in Eastern Research Group's "Review of Biosimilars Biologic Product Applications - Study of Workload Volume and Full Costs" (Table ES-2). Projected FTEs calculated by doubling the FY15 estimated calculated through Q2 (March 31, 2015).

The increase in FTE expenditure is a direct reflection of the change and increase in workload in fiscal year 2015. To date, there are four companies that have publicly announced submission to FDA of a total of five applications (351(k) Biologics License Applications (BLA)) for proposed biosimilar products. To date, FDA has approved one of these 351(k) BLAs for a biosimilar product, Zarxio (filgrastim-sndz).

FDA will continue to need to hire and train additional staff to support this program. As the BsUFA program matures, FDA expects overall BsUFA performance metrics will improve in coming years.

GLOBAL DEVELOPMENT

Beyond our borders, we continue to support global development of biologics and biosimilars, and are actively engaged with other national regulatory agencies. We recognize that biosimilar development and regulation are of interest worldwide and FDA can be a leader in this arena. Thus, FDA is an active participant in international regulatory organizations and at meetings and scientific conferences.

FDA has also worked to ease the burden for sponsors of proposed biosimilar products that have previously been approved outside the United States, such as in the European Union, to develop their proposed biosimilar products for the U.S. market. The BPCI Act requires a demonstration of biosimilarity to a U.S.-licensed reference product. This requirement was initially perceived as a barrier to development that necessitated conducting multiple separate studies with a regionally approved comparator product. As a global leader, FDA took steps to address this issue in a scientifically rigorous manner by issuing guidance describing the use of a non-U.S.-licensed comparator in certain studies based on an adequate scientific bridge between the U.S.-licensed reference product and a non-U.S.-licensed comparator product. Following FDA's publication of draft guidance on this topic, the European Medicines Agency adopted the same regulatory approach with the same scientific standards. While, as noted above, the BPCI Act requires a demonstration of biosimilarity to a U.S.-licensed reference product, and as a scientific matter, a sponsor will need to directly compare its proposed biosimilar product with the U.S.-licensed reference product in certain studies, the scientific approach outlined above should help prevent unnecessary duplication of other studies.

EDUCATION AND OUTREACH

As previously noted, stakeholder confidence is essential to the success of the biosimilar program. FDA has and will continue to actively engage with stakeholders. We have held public and stakeholder meetings. FDA also is undertaking a multi-phase plan for communicating with stakeholders and educating them about biosimilars. The first phase of the communication plan is to lay a solid foundation with understandable definitions and descriptions that health care professionals and

consumers can easily understand and adopt. To help guide message development, FDA has a contract to conduct a focus group study of prescriber and pharmacist knowledge of biosimilar biological products. FDA also has a contract for Web-based training programs, which includes a biosimilar course to educate health care professionals (physicians, nurses, pharmacists, nurse practitioners and physician assistants) nationwide. FDA plans to communicate information in various formats to consumers as more biosimilar products are approved and enter the marketplace. We will continue our outreach activities, including interacting with physicians and pharmacists and educating consumers and patients, well into the future.

THE PATH FORWARD

Of course, more work needs to be done. FDA will continue to meet with companies to provide advice for individual development programs. Over the past year, we have seen the number of meeting requests and marketing applications grow. We are excited about this growing demand, and we will continue to facilitate development, submission, and timely review of biosimilar product applications.

Even with our challenges, we are optimistic and energized about the future. This new pathway for biosimilars and interchangeables has the potential to offer a significant contribution to the public health of many Americans. At FDA, we are working hard to ensure this impact can be realized. Thank you for inviting me here to highlight the impact of this important law. I look forward to your questions.

Senator CASSIDY. Dr. Woodcock, I mentioned briefly interchangeability.

Dr. WOODCOCK. Yes.

Senator CASSIDY. The ultimate in biosimilarity if you will. First let me say, as I've told you privately, the questions I'm asking are basically questions that people on the outside have submitted. I feel as if I'm a conduit and selected from them.

No. 1, is the concern that FDA still has not provided details on the specifics of interchangeable products. Broadly what would qualify in your mind as interchangeable? And No. 2, can we get there?

Dr. WOODCOCK. First let me answer your second question. We believe that getting there is both scientifically and practically feasible and we're going to get there.

Senator CASSIDY. OK.

Dr. WOODCOCK. All right. However, let me tell you what the statute that Congress passed says interchangeability is first. First of all, it's expected to produce the same clinical result as the referenced product in any given patient. Second of all, we need to find that a product that is administered more than once to an individual the risks in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar product, I'm paraphrasing, and it's referenced product is not greater than using the reference product alone. We have to make an interpretation of that statutory standard. That is the statutory standard and it sets a high bar.

The reason for the basic reason is the human immune response. All right. Because when we approve a biosimilar as a biosimilar we are going to find that it is highly similar to the reference product. Meaning that it's expected to produce the same clinical effects, both safety and efficacy. However, that raises a question if what happens in our current healthcare system say with generics you're a patient and you go get your medicine and you're switched over and over again between one generic or another, or sometimes you might get the reference drug, the question is would that cause additional harm because of unexpected immune responses. Because unlike most of our small molecule drugs, the body recognizes these large protein molecules that are biosimilars and often in some people will

make an immune response. What the concern has been is that this continued switching could raise that immunity, sort of provide a booster effect and cause unthwarted effects.

There have been several episodes with one biosimilar drug, erythropoietin, where people made antibodies based on some small manufacturing changes. This is in the reference world, not the biosimilar world. People then had antibodies against their own hormone erythropoietin and it resulted in something called pure red cell aplasia and meant that they would be transfusion dependent for the rest of their lives.

Senator CASSIDY. Can I interrupt?

Dr. WOODCOCK. Yes.

Senator CASSIDY. Because I think you've just done a nice job of showing that the products may not be similar. On the other hand, you had mentioned in our private conversation, and I mentioned in my statement, that one batch to the next batch of a reference drug might be different.

Dr. WOODCOCK. That's correct.

Senator CASSIDY. Clearly you can have a little bit of wiggle room and presumably you don't want to develop that.

What I've been told is that the fingerprinting, if you will, the ability to really look at the nature, the structure, the thermodynamic kind of configuration of some of these biosimilars is now progressing to the point that you can establish how these are twins almost. A little freckle here, not there, but otherwise a twin. With that in mind, in your regulator guidance where you kind of create a possibility for this advancement in the ability to show similarity biochemically, et cetera, as part of the way in which you would establish interchangeability?

Dr. WOODCOCK. We certainly do in a degree to which something is highly similar and as similar to a fingerprint level would be a very strong point in favor. Our problem is the human immune system is capable of detecting tiny variability.

Senator CASSIDY. So the freckle makes a difference?

Dr. WOODCOCK. Perhaps. Not usually. As you said, not usually. The problems I was talking about were from a reference product. They were between different versions of a reference product, not a biosimilar.

Senator CASSIDY. Inherently though you're saying that the degree of variability even within a reference product means that you may get an immune difference, and it may not matter that it's an interchangeable drug. It could have been that the same innovator drug continued to have been given would have induced the same effect.

Dr. WOODCOCK. These had very small manufacturing changes we believe that brought on these problems.

Senator CASSIDY. OK. I thank you.

I now turn to my Ranking Member.

Senator MURPHY. Thank you very much, Senator Cassidy.

We talked about the certainty that the industry needs to start populating the field with more biosimilars. You've mentioned that you have on your guidance agenda for 2015 guidances including interchangeability and labeling. Are we still on track to see those by the end of the year?

Dr. WOODCOCK. We are working very hard to get them out, but I never give a date for guidances because it's sort of out of my hands. There's multiple clearances involved and these are very complex. We are working very hard on these.

Senator MURPHY. I've heard a lot about a proposal from CMS to blend reimbursement for biosimilars of the same reference product, and I'm hoping you can talk a little bit about this and whether you can tell us whether assigning the same CMS billing code is going to impact their use in FDA's opinion.

Dr. WOODCOCK. CMS billing codes are often used by us, as well as of course for other purposes, but they're used for tracking purposes so we can determine who got what drug. Right. CMS has a proposed rule. They're still in the rulemaking process. If CMS were to finalize this proposal, FDA and CMS are developing an approach to use sub codes, or what are called coding modifiers. These already exist in the CMS world. That would help us distinguish who got what. They would distinguish amongst the various biosimilars if there were multiple biosimilars.

Senator MURPHY. I wanted to talk to you a little bit about education. It took us a long time to educate both providers and patients about chemical generics. It was really well after the passage of Hatch-Waxman that there was a level of comfort. And, given the substantial differences that we've talked about and the amount of money that the pharmaceutical companies are going to put behind marketing campaigns to tell both doctors and patients that they shouldn't take the generic, who's responsible for the education necessary to provide the level of comfort ultimately in the biosimilar space that I would argue we have today in the chemical generic market? Because there is just going to be all sorts of opportunity for the owners of that original patent to flood the healthcare space with bad information about why you shouldn't take that biosimilar, so I think you referenced in your testimony this issue of education. Talk to us a little bit about once we have more than one, how we're going to go about that campaign of getting the truth out there about biosimilars.

Dr. WOODCOCK. Yes, well I think to a great extent this does fall on FDA's shoulders, and also to a great extent as they say it's déjà vu all over again because we did go through this, and we are still going through this with generics with some subspecialty groups. Actually we've been doing trials to show equivalence of generics in the seizure area.

We have laid out a plan of campaigns of education, and we're also doing focus groups and other activities to determine what is the current level of understanding and what do people need to know. My experience, if I may, is that we're going to have to target the subspecialty groups one by one. Most clinicians are overwhelmed with people who want to educate them about things. We are going to be offering CME type of credits, courses, and so forth. We can go subspecialty by subspecialty as we approve biosimilars that are targeted and used by a certain subspecialty group. They're not used generally by all practitioners. They're also State legislatures and others who are very interested. Of course this is a very complicated issue. We have a menu of educational activities planned out of the next several years.

Senator MURPHY. I know this is an issue that doesn't necessary fit natural to Congress to be funding physician and provider education, but we're talking about next year reports suggesting that 8 of the top 10 drugs on the market are going to be biosimilars. They cost on average 22 times that of traditional drugs. If we are successful in getting this pathway to biosimilars moving then my fear is with a product sitting on the market that could cost 30 percent less we were are going to be behind this avalanche of pharmaceutical advertising that will keep the market away from the biosimilars.

I just hope it's a topic for conversation here in this committee. We can do all of this work on trying to make sure that we approve biosimilars, but if they're not actually getting prescribed, if we aren't giving FDA the resources to make the case that they should be prescribed, we're going to be spending billions and billions of additional dollars that we don't need to simply because we're continuing to funnel money to the makers of the original product who are in competition with the maker of the biosimilar.

Thank you, Mr. Chairman.

Senator CASSIDY. Next will be Senator Scott. And just to acknowledge that the Chairman is here and he would normally go first, but he says just go in the order. The order will be Senator Scott, Senator Warren, Senator Alexander then Senator Kirk.

STATEMENT OF SENATOR SCOTT

Senator SCOTT. Thank you, Mr. Chairman. Thank you, Mr. Chairman.

Good morning, Dr. Woodcock. Thanks for being here. My question really goes to the issue of labeling the biosimilars versus the biologics. It appears to me that early on the goal was to make sure that the biosimilars were specifically and correctly labeled so that there would be no question about what it was. It seems like shortly thereafter or at least in 2012 the purple book play book basically comes out that says that doctors can go online to figure out what it really is as opposed to sticking with the clearly specifically labeled drug itself. Why the change?

Dr. WOODCOCK. We haven't really made a change. We did not put anything in that final guidance because it really wasn't about labeling. We plan to issue a labeling guidance. We also have a citizen petition before us from AbbVie on a variety of these issues that's in the docket. We are evaluating that as we evaluate what we're going to put into our guidance.

Senator SCOTT. I think to some extent Senator Murphy started having the conversation about the appropriate education necessary for the clinicians putting them in the position where when you look at the absolute onslaught of work that we're putting on the backs of doctors to find them having to deal with a new 68,000 different billing codes versus four or five previously.

Dr. WOODCOCK. Right.

Senator SCOTT. You look at the audits that are coming forward. You look at the medical records that are online or electronic medical records which seems to be a catastrophe for many physicians. We had a hearing here recently and so to not take the original intent on the first biosimilar immediately as it's coming out seems

to me to be a costly delay in the impact that it could have on patients.

I have had the unfortunate experience of going to a doctor to get a prescription for medicine, and when I called my pharmacist she tells me that the two medicines that the doctor was giving me actually could have a negative impact on my liver. And so she said, "Immediately stop taking that medicine."

My concern is that as there is a delay in making a clear decision on the labeling and the importance of labeling that we may find ourselves with more patients being harmed. Frankly, if we're looking for a way, as Senator Murphy has inferred to controlling and/or reducing the cost, whether it's 30 percent or 20 percent, these can be very expensive, the fact of the matter is that the clarity needed for the industry so that they can make economic decisions is incredibly important.

I would just go back to my original question. What can we anticipate and/or expect as it relates to labeling on the biosimilars, and when can we expect it?

Dr. WOODCOCK. I can answer the when because it's still under consideration. I can't answer the what. We hope to do that as soon as possible. We understand the criticality of this issue. It's really important for us to gain and maintain the trust of the healthcare community in these products. Right now the biosimilar that we approve is not interchangeable. A clinician will have to write for that for a patient to get it just like they would for any other drug. They can write with the brand name or they can write with the proper name of the biosimilar product.

Senator SCOTT. It seems like doctor or Senator Cassidy over there suggested that the biologics and the biosimilars could be somewhat like twins. My real question from your answer would suggest that these are identical twins and not paternal twins. The fact of the matter is that the similarity of the drugs may be important. If they are not interchangeable at this point it's important for us to give the appropriate indications going down the road, and it appears to me that the best time to do that is immediately. And if the answer for as soon as possible seems like the timeline would then be to be determined.

Dr. WOODCOCK. There are tradeoffs involved in various labeling decisions.

Senator SCOTT. Yes, ma'am.

Dr. WOODCOCK. We have a citizen petition that goes through some of those. There are folks on either side of this issue. We need to have a labeling convention that maintains the trust of the clinicians. I understand they want to know what their patients are getting.

Senator SCOTT. That's important.

Dr. WOODCOCK. Right now you have to write a prescription for the new biosimilar—

Senator SCOTT. Yes.

Dr. WOODCOCK [continuing]. In order for a patient to get it. They will know that the patient is getting that biosimilar medicine. It is expected right now to deliver the same clinical effects as the reference product.

Senator SCOTT. At this point you are saying the biologic and the biosimilar are interchangeable and therefore more like the name brand and the generic versus the concerns that I have as it relates to the specificity of the way that the drug interacts with the individual patient?

Dr. WOODCOCK. They are not interchangeable because we haven't determined the immune response issues. However, they will give the same clinical effect. We had an advisory committee. They voted overwhelmingly that they are biosimilar.

Senator SCOTT. My last comment would be that I know that you've been dedicated to this cause for it sounds like nearly 20 years. I would hope that we would be able to get appropriate labeling if we've been working on this concept and getting to this point for the last two decades. We could start off with appropriate labeling maybe even day one if we've been on this road for 20 years. I know government moves slow.

Senator CASSIDY. Senator Warren.

STATEMENT OF SENATOR WARREN

Senator WARREN. Thank you, Mr. Chairman.

Thank you for being here, Dr. Woodcock. Biologic drugs, complex products like enzymes and antibodies, are great medical achievements that allow people to live longer, healthier lives. These drugs are extremely expensive. According to IMS Health, biologics accounted for 28 percent of all drug spending in 2013 and we know that this number is rising. Medicare has also been hit hard. According to the GAO, just eight biologic drugs—just eight drugs—account for over 40 percent of all Medicare Part B spending.

The good news is that the Affordable Care Act established a pathway for biosimilar drugs that, according to a RAND analysis, have the potential to save us about \$44 billion over the next 10 years. We know from our experience with ordinary generics that significant cost reductions for drugs don't occur until two or more follow-on competitors come to market. In order to foster a robust biosimilars market that is actually going to drive down the cost of these drugs, drug makers need to know the rules of the road so they know whether or not to enter this market.

Dr. Woodcock, it has now been 5 years since Congress authorized the biosimilars pathway, but so far the FDA hasn't even produced a draft guidance describing the standard for an interchangeable biosimilar. In addition, the FDA has not released guidance on how the products will be labeled and has not finalized many other guidance documents that will help companies enter the biosimilars market.

Can you help us understand why the FDA has not completed this work in 5 years?

Dr. WOODCOCK. We have a biosimilar program and we have spent a lot of time. We have 57 products in development, and we have been giving those sponsors one-to-one advice. There are 16 different reference-listed drugs. So 57 products, 16 reference-listed drugs, you can see if these products get across the finish line we will have competition.

Senator WARREN. I appreciate that. But, the question is it's been 5 years now? In doing this, you know, the European Medicines

Agency adopted a biosimilars pathway in 2003 and approved the first biosimilars in 2006 for the European Union. Health Canada approved its first biosimilar in 2009. The FDA is building on nearly a decade of experience within the European Union, as well as experience from Canada, and yet, 5 years have gone by and we still don't have any of these guidelines out not even in draft form.

Dr. WOODCOCK. We've issued three final guidances and one of them is the foundational guidance for how you develop a biosimilar, which is the scientific considerations. It put forth the scientific framework for what the companies needed to do to start. Because the statute rightly said that the comparison had to be a U.S. reference-listed drug and many of these sponsors had to start by comparing to the U.S. drug, which might be different than the European reference-listed drug.

We gave a scientific structure and a framework that said that the foundation is the analytical similarity and that other types of studies were put on top of that. The amount of clinical data needed depended on how much uncertainty remained about biosimilarity after doing that program. These 57 sponsors are engaged in the scientific program.

Senator WARREN. No, I'm sorry, Dr. Woodcock. I appreciate that there is a process, and that's what I'm hearing you say over and over and over. The real question that I'm pushing on is that it is time now to get this done. The longer it takes you to set the rules the longer patients will be stuck paying for only one very expensive option to treat their medical needs.

There aren't very many things in Washington that stakeholders on both sides of the aisle agree on and that people out in industry agree on. I think we all agree that it is time to get guidance documents.

If the Chair will indulge me? I've got just a few seconds left. I want to go back to this question about generics, if I can.

Biosimilars can save an estimated \$44 billion over the next 10 years, but that will happen only if patients have confidence in the quality of the biosimilars and their doctors have confidence—

Dr. WOODCOCK. That is correct.

Senator WARREN [continuing]. And will actually prescribe them.

We know from the very established generic drug market that it suffers from severe misperceptions here. Studies by researchers at Harvard found that nearly 23 percent of physicians had negative perceptions about the efficacy of generics and nearly 50 percent had negative perceptions about quality. They also found that about 30 percent of patients felt that brand name drugs were going to be more effective than their generic counterparts. This is for some drugs that have been around for a very, very long time.

Given the newness and the complexity of biosimilar drugs, I'm concerned that misunderstandings about biosimilars could hamper their uptake in the market. I understand that you're currently conducting research. You said you're starting to lay out a plan for how to deal with the public perception of biosimilars. I just want to underline the urgency of this. Generics have been on the market for 30 years since Hatch-Waxman opened up the generic market, and yet even today this is not a fully open market where physicians will prescribe and where patients have confidence in the drug.

I want to hear what it is that you're planning to do. If you could just give me something that's specific about dealing with the potential negative perceptions of biosimilars? We've got to create a market here that works.

Dr. WOODCOCK. Do I have time to answer?

Senator WARREN. Is that all right? Could she? Is that all right? Thank you. I appreciate the indulgence.

Dr. WOODCOCK. First of all, let me say we have to get the science right so we can't have problems with the first biosimilars out of the block or we will cause—

Senator WARREN. I totally understand that.

Dr. WOODCOCK. OK.

Senator WARREN. That's why we need guidelines as well.

Dr. WOODCOCK. The guidances that you're talking about are about more policy issues. They are not about the scientific standards. We've issued eight guidances: three final and five draft guidances.

Senator WARREN. I'm looking here at the documents that say, "A draft guidance for describing the standard for interchangeable biosimilars is not out."

Dr. WOODCOCK. That's correct.

Senator WARREN. We've got to have those. I get that you want to get those. We also need a plan in place that's going to educate physicians, that's going to educate the public because there really will be confidence that this work.

Senator CASSIDY. Senator Warren, I think we'll—

Senator WARREN. I have used my time.

Senator CASSIDY [continuing]. Probably have a second—

Senator WARREN. The Chair has been most indulgent.

Senator CASSIDY. Thank you.

Senator WARREN. I will stop. Thank you, Mr. Chairman.

Senator CASSIDY. Mr. Chairman.

STATEMENT OF SENATOR ALEXANDER

The CHAIRMAN. Thanks, Senator Cassidy. Thanks to you and Senator Murphy for leading this hearing. This is important and I've enjoyed the questions. I thank Dr. Woodcock. She's got a big job. She's done it for a long time and we appreciate her service to the country.

I'm here mainly to listen and learn more about biosimilars. I think that comparing the experience between generics and biosimilars is useful to me as I try to understand this. I think Senator Warren's questions about the marketplace are pretty good questions and right to the point.

I have really two questions. Only two. First, is there anything that you would like for us to do, which would make it easier for you to do what Senator Warren was just asking about? Is there anything that we can do to create an environment where you're more likely to succeed in introducing biosimilars to a robust marketplace more rapidly, safely, and so we can fulfill the promise of them, which I know you want to do and which we want to do?

My second question is, what are the most important guidance documents? You've got a lot of guidance documents that you could put out. If you were thinking about the most important ones that

need to come out next what are they and how soon do you plan to release those?

Dr. WOODCOCK. For your first question we have the resource use of this program. The resources that are available to it and the testimony, and in appropriate dollars there's about \$21 million. We're talking about savings of millions of dollars here. This program didn't contemplate funding for large educational campaign to the outside world.

We are really highly fully occupied on the 57 development programs and the 27 other groups that have come and talked to us about developing individual products plus developing the guidances and the legal, regulatory, scientific, and policy framework for how we're going to do this that'll stand up to legal challenge and also the scrutiny of the scientific community.

I agree with the committee that the most important next guidances would be interchangeability and labeling and finalizing our naming guidance so that people know although that is an issue for the outside world. It's not a scientific issue, per say. The most important thing we had to do was set the scientific framework that's bullet proof, OK, that will earn the trust of the community and will actually work to provide biosimilars that are safe, and effective, and have the same properties as an innovator. That was most important, No. 1.

Clearly we have to conduct the education and we need to get out all of the framework, not just the fundamental building blocks, but how do you prove interchangeability. Of course we're talking to all of these 57 sponsors about how they will show interchangeability, right. We're learning from that. They're learning. What we're learning is that each of these 57 products is a little bit different. And so we are learning a lot from this experience.

There is no doubt that those are very important that we get out, and we will try to get them out expeditiously.

Senator CASSIDY. Senator Kirk.

STATEMENT OF SENATOR KIRK

Senator KIRK. Thank you. I have one question. Do you believe that further guidance is in the interest of doctors and patients?

Dr. WOODCOCK. The guidance is mainly going to be directed at industry other than the labeling and naming conventions, obviously which will be of great interest to the healthcare community. The scientific framework is directed toward the industry. What do you have to do to show that your product is first biosimilar, which we have put out a guidance on, and interchangeable?

Senator KIRK. Let me just sign on with Senator Warren saying that I also agree with her feelings about how quick the Canadians and the Europeans have been. I think that the United States should be able to keep up with those guys.

Dr. WOODCOCK. I will say that the Europeans had a 6-year start on us, and some of the products they approved right away had been approved in the United States for some time because a number of these we did not approve as biological products. We approved them as drugs. We were able to put basically similar versions on the market because the drugs law has had that and regulations have had those provisions for a long time. It wasn't present in Europe.

Senator KIRK. Thank you, Mr. Chairman.

Senator CASSIDY. We should have kept it as drugs, huh? The what? What's that? The Chairman wishes to know how many products are like that that got approved under the previous?

Dr. WOODCOCK. I'd have to get back to you. Omnitrope is a good example growth hormone. I don't remember exactly when we approved that. It might have been In 2004 possibly or 1905. We don't know. We don't know offhand. We had approved that and it was on the market already. That's an example. The growth hormones are an example. Insulin is an example. There are a number of others.

Senator CASSIDY. Interferon.

Dr. WOODCOCK. Interferon was approved as a biologic. I approved that when I was over in CDER.

Senator CASSIDY. OK. Senator Hatch.

STATEMENT OF SENATOR HATCH

Senator HATCH. Thank you.

Welcome. I'm very pleased with what you do over there, and I'm particularly pleased with what you're doing in this area.

Dr. WOODCOCK. Thank you.

Senator HATCH. Let me just ask you a couple of questions that have bothered me. When FDA approved Phaxio they designated the placeholder suffix that indicated the name of the company. The draft guidance of FDA just issued on naming though provides a random letter suffix.

Dr. WOODCOCK. Right.

Senator HATCH. What was the FDA's thinking that lead to this particular change? It's just interesting to me.

Dr. WOODCOCK. There are a lot of tradeoffs in the naming convention.

Senator HATCH. Yes.

Dr. WOODCOCK. We want to be able to know what people go, so if there is some severe problem out there we won't have to take every single one off the market. We can deal with the one that's causing the problem. We want to be able to uniquely identify them. There's concern that uniquely identifying them may inhibit switching when interchangeability becomes a reality. With those tradeoffs there are a lot of different opinions about what should be done.

In the guidance that we're putting out we ask should we have the company contraction as the suffix or should we have the random four letter suffix. So we're asking about that.

The first one out of the box had the contraction of the company. That one is easier to remember, obviously, but also then it's tied to that company. If the product is sold or transferred or—you know there are different tradeoffs involved if you start thinking through how you do the suffix. We didn't know the right answer, and there are a lot of different issues. In the guidance we're also asking about interchangeables. Should they have the same suffix as the reference drug or should they retain their unique substance. There are tradeoffs there too.

Senator HATCH. Is it possible for FDA to trace adverse events and identify the source without a unique identifier in the name?

Dr. WOODCOCK. Currently, no. Not in all settings. A lot of these, as Senator Warren was talking about, are administered in the hospital. In a hospital they don't have the NDC code that we can track. We need a different way to be able to track them when they're administered in settings where they're billed a different way. We must be able to figure out which drug is causing a problem.

Senator HATCH. Has FDA analyzed, No. 1, the extent to which these cost of changing names is passed on to healthcare payers and consumers? Or, No. 2, the extent to which passed through costs will be offset by savings from biosimilar competition created as the result of this policy?

Dr. WOODCOCK. We believe there will be some costs—

Senator HATCH. Yes.

Dr. WOODCOCK [continuing]. In it for the innovators to put the suffix onto their drugs if that is the policy that is arrived at the end based on our proposed rule. There is an analysis of cost accompanying that.

Senator HATCH. OK. Given the similarity between FDA's draft guidance and the World Health Organization's scheme on biologics qualifiers, it would be important to consult with a WHO in arriving at a global solution. Could you please comment on how the agency is consulting with the WHL and on what aspects we're consulting with them?

Dr. WOODCOCK. Certainly. We work with and meet with the INN committee and the committee on naming at WHO. We have long been a part of that. We are aware of the convention that they're considering now. Certainly we have exchanged views with them and have talked to them about that. I am certainly aware of the desirability of a common global standard for how this naming is going to proceed. However, if you look around the world you'll see that people have been shifting over time to different conventions.

Right now, in the EU, prescribers are required to identify the product by the brand name because they started out with the same name, and now they have to put the brand name and the lot number in the chart for pharmacovigilance purposes. That would not be a good solution in the United States. The WHO convention they're discussing is very similar to what is proposed inter-guidance.

Senator HATCH. Thank you. I appreciate the work you're doing very, very much. This is an area of great interest to me as you know. Thank you.

Senator CASSIDY. Thank you, Senator Hatch.

Dr. Woodcock, I think they're calling votes or maybe they're going into session and they'll call votes shortly. If we can, each of us just go with a couple of more questions, if that's OK?

Dr. WOODCOCK. Certainly.

Senator CASSIDY. Going back to the interchangeability aspect of it, this is a question I was asked to ask. From a biosimilars developer's point of view, the lack of guidance on statistical approaches to analytical similarity has been the most problematic issue to deal with due both to the lack of transparency on what the requirements are and the evolution of your thinking.

Dr. WOODCOCK. Yes.

Senator CASSIDY. It's clear from what you're saying that thinking has evolved.

Dr. WOODCOCK. Yes.

Senator CASSIDY. The questions are, the guidance on the statistical approaches to analytical similarity is particularly important as it impacts initial improvability as a biosimilar under the 351K, when is the agency planning to issue this specifically? And then related to that, what level of consultation has the agency had on statistical approaches to analytical similarity in consultation with EMA, Health Canada, and the PMDA?

Dr. WOODCOCK. Certainly. This is part of the foundational work in determining biosimilarity and the statistical approaches to analytical similarity is the third guidance after interchangeability and naming that we need to get out as soon as possible.

What is this and why do we need it? As you said, the innovator drug, the reference drug can vary from lot to lot in its characteristics. That's a statistical matter of how much variability there is in that reference drug. Then the biosimilar drug can vary. We have to decide how much those confidence limits need to overlap for us to declare them biosimilar. This is of course a matter of analytical chemistry and statistics.

We have really world class experts working on this. They have consulted with the EU and we certainly are of like mind with the EU. I think they think our approach is sound. We hope to get that guidance out quickly.

We do not believe that rigid limits, such as we have in the generics world for bioavailability or bioequivalence it's called, are appropriate in this setting. This is going to be a more flexible standard. We need to tell people how to run these statistics and how to—

Senator CASSIDY. You say quickly. Can you give a sense of end of the year?

Dr. WOODCOCK. I would hope within the next 6 months.

Senator CASSIDY. OK. Then related to that, a question I realize that comes up, it's almost as if you have a suffix that there truly is not a nonproprietary name in the most meaningful sense of that. If I'm a physician and I write for a generic nonproprietary name, but I'm required to put a suffix does that mean that effectively I'm telling the pharmacist that he or she must use that particular one as designated by the suffix? Or the fact that I'm merely using the root, if you will, do they allow them then to change between those with different whatever the pool is of suffix?

Dr. WOODCOCK. Right. There are two tiers to this. One is we'd have to find them interchangeable first, OK. If we found something interchangeable then State law will govern pharmacy substitution.

Senator CASSIDY. If there's four different products with four different suffixes then here's the innovator drug and here is the one that is deemed interchangeable, so the pharmacist would have to know that these two are not deemed interchangeable. If the pharmacist wishes to change it can only be for this one with this suffix, correct?

Dr. WOODCOCK. That's correct. That's the use of the purple book. Right now for generics we use the orange book, and that's sort of the bible because it has the ratings. Are they interchangeable rat-

ings because some drugs will not be rated interchangeable. The pharmacist looks there and can determine substitutability. We're going to have a purple book for the biosimilars because they're going to have the same set of issues.

Senator CASSIDY. Let me quickly ask as well. There's concern that some of the manufacturing plants in India have had very poor standards. We've discussed this before in a previous ENC committee hearing when I was on the other side. There's been some kind of you rapping knuckles at FDA in regards to recent productions not using good manufacturing practices, and yet it doesn't seem there's been follow through on that. Since the biologics are particularly an issue here, any thoughts on how we're going to guarantee that those products produced in places like India are safe?

Dr. WOODCOCK. Currently we think some biologic products are filled in India, but we don't know of any that are produced there that are actually destined for the U.S. markets as far as the actual making of the biologic itself. The laws around and the regulations around biological products are very stringent as far as manufacturing because of the long checkered history of problems that actually originated in the Public Health Service Act.

As with any biosimilar or any biological product, wherever it's produced, we go out and inspect all of the facilities unless they've been very recently inspected. We send someone from our laboratories and usually another person from the Office of Pharmaceutical Quality to go out and participate on those inspections. The manufacturing is very carefully regulated.

Senator CASSIDY. You told us last year in ENC though that you had a difficult time inspecting plants in India. There was an issue of whether or not the union contracts allowed designation, et cetera. Is that no longer a problem?

Dr. WOODCOCK. We have the ORA, the field organization has developed a foreign inspectorate and has more people whose job it is to actually go out and inspect foreign facilities. A lot of that has to do with the generics program and the requirement for parity of inspection between United States and ex-United States, which for me is a very welcomed development. We also have an office in India. I think we're doing a very thorough job.

The biologics are different, but they are inspected very carefully because of the difficulties in manufacturing.

Senator CASSIDY. Yes. Senator Murphy.

Senator MURPHY. Thank you, Mr. Chairman.

I have a massive feeling of inferiority on this panel with a practicing physician who knows so much about this issue and the father of the modern generics industry around the corner.

I just have one additional question and it's back to this issue of looking ahead to potential barriers to the utilization of generics. We've got about 31 States that have considered State laws around how biosimilars would be provided to patients and they're all different, but they have some common characteristics.

I guess my just very broad question to you is as FDA has looked at these laws do you view them as facilitating the biosimilar market, or in some cases are some of these laws actually providing bar-

riers or, you know, building in that potential discriminatory behavior that we worry would present a barrier?

Dr. WOODCOCK. There is patchwork and some of them are facilitatory and some of them may actually cause barriers. Senator Hatch will know we saw this at the dawn of the generic age. There were many State laws passed that actually forbade substitution of certain generics and so forth. We've gotten over that, but it does take earning the trust and continuing to maintain the trust of the clinical community about this program—that it is scientifically sound and that their patients are not going to suffer at all if they get a biosimilar. They'll get the same clinical effect.

Senator MURPHY. What's the interaction that FDA has with the State legislatures that are devising these laws?

Dr. WOODCOCK. We've been asked for explanations of what the programs are, but we do have an intergovernmental affairs office that interacts with the States.

Senator MURPHY. Interesting. Encourage that team to be proactive in their approach. Thirty-one States is going to be 50 States very soon. If we get a whole rash of State laws that erect barriers it doesn't really matter what education you do if the law prevents the usage of these biosimilars.

Dr. WOODCOCK. Yes, and we're seeing that patchwork in Europe even though they're 6 years ahead with their statutory framework. The interchangeability is administered by the different countries and it's quite different across Europe.

Senator MURPHY. Thank you. Thank you, Mr. Chairman.

Senator CASSIDY. Dr. Woodcock, I think I'm supposed to have a script here as to what I'm supposed to say next.

The hearing record will remain open for 10 days. Members may submit additional information for the record within that time if they would like.

Thank you for being here.

The committee will stand adjourned.

Dr. WOODCOCK. Thank you.

[Additional Material follows.]

ADDITIONAL MATERIAL

FOOD AND DRUG ADMINISTRATION,
SILVER SPRING, MD 20993,
May 9, 2016.

Hon. BILL CASSIDY, M.D., *Acting Chairman,*
Committee on Health, Education, Labor, and Pensions,
U.S. Senate,
Washington, DC. 20510-6300.

DEAR MR. CHAIRMAN: Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the September 17, 2015, hearing before the Committee on Health, Education, Labor, and Pensions, entitled “Biosimilars Implementation: A Progress Report from FDA.” This is the response for the record to questions posed by several committee members, in a letter we received on November 2, 2015.

Please let us know if you have any further questions.

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

Sincerely,

DAYLE CRISTINZIO,
Acting Associate Commissioner
for Legislation.

cc: The Honorable Lamar Alexander, Chairman.

RESPONSE BY THE FOOD AND DRUG ADMINISTRATION TO QUESTIONS OF SENATOR ALEXANDER, SENATOR COLLINS, SENATOR KIRK, SENATOR HATCH AND SENATOR CASSIDY

SENATOR ALEXANDER

Question 1a. 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.

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?

Answer 1. 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).

Question 1b. 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)?

Answer 1b. 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, mecasecmin products, pancrelipase products, pegademase products, pegvisomant products, sacrosidase products, somatotropin 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.

Question 1c. 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?

Answer 1c. 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.

Question 1d. 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 to its reference product, given the complexity and variation inherent in the development of follow-on biological products.

Answer 1d. 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)). Because of the complexity of protein molecules and limitations of current analytical methods, it would be difficult for manufacturers of proposed protein products to demonstrate that the active ingredient in their proposed product is identical to the active ingredient in an already approved product.

Question 2a. 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 biosimilar, 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.

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”?

Answer 2a. 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 guidance¹ 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.”

Question 2b. 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?

Answer 2b. 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 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.”

Question 2c. Does the FDA consider the Purple Book to be a part of a biological product’s labeling?

Answer 2c. 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.

Question 2d. 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?

Answer 2d. 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 prod-

¹“Scientific Consideration in Demonstrating Biosimilarity to a Reference Product,” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

uct 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.

Question 3a. 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.

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?

Answer 3a. 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, 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, FDA issued a draft guidance on labeling for biosimilar products.

Question 3b. What postmarket surveillance will FDA require for extrapolated indications? How, if at all, will the requirements vary by circumstance?

Answer 3b. 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.

Question 3c. Under what circumstances would FDA rescind approval for an extrapolated indication? What procedural requirements and evidentiary standards would apply?

Answer 3c. 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.

Question 4a. Please identify the requirements for manufacturing practices and inspections that apply to manufacturers of biological products, including biosimilars.

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

Answer 4a. The nature of small molecule drug and biologics product inspections do not differ in approach as each inspection is conducted in accordance with a Compliance Program, which provides instructions 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 followup 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 (FDASIA) 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.

Question 4b. Is the manufacturer of a biological product subject to requirements that differ from those applicable to the manufacturer of a small molecule drug?

Answer 4b. 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.

Question 4c. If a biological product is approved as a new drug rather than licensed as a biological product, does it affect which requirements apply?

Answer 4c. 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.

Question 4d. 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?

Answer 4d. 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.

Question 5. 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?

Answer 5. 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 consumer² and health care professional³ 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 Update⁴ 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 increase health care provider and consumer confidence in this new category of products. However, additional resources for education and outreach would enhance these efforts.

Question 6a. 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.

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?

Answer 6a. 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 the 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.

²<http://www.fda.gov/Drugs/developmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm>.

³<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm>.

⁴<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm>.

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.

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

Question 6b. 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?

Answer 6b. 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.

Question 6c. 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?

Answer 6c. 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.

SENATOR COLLINS

Question 1. Generic utilization in the United States has reached 86 percent since the enactment of the Hatch-Waxman Act in 1984, but it took many years for utilization to reach that point. One of the keys in increasing generic utilization was ensuring that the public, as well as healthcare providers, had confidence in the safety and efficacy of FDA-approved generic drugs, which can help keep rising drug costs in check. It will be important that healthcare providers and patients have that same confidence in the safety and efficacy of FDA-approved biosimilars.

Dr. Woodcock, you mentioned in your written testimony that stakeholder confidence is essential to the success of the biosimilar program. Can you elaborate on the types of public education efforts that the FDA has and will engage in around biosimilars?

Answer 1. 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 Zaxio approval, FDA updated its website to provide more information about biosimilar products, including pages specifically for consumer⁵ and health care professional⁶ audiences. The content includes definitions of biosimilar products and interchangeable products, information on how health care pro-

⁵ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm>.

⁶ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241719.htm>.

professionals can prescribe these products, and the differences between biosimilar products and generic drugs.

FDA also released a Consumer Update⁷ 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 as more biosimilar products are approved and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability.

In addition to developing communication materials, as part of its multi-phase plan, FDA is conducting research on prescriber's knowledge and perceptions of biosimilar products. This research will help inform future outreach and education efforts to both health care professionals and consumers. Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to increase health care provider and consumer confidence in this new category of products.

Question 2. FDA has announced that it expects to release a draft guidance on the framework for labeling biosimilars in 2015. For both biologics and biosimilars, healthcare professionals have mentioned the need for access to reliable information that is directly relevant to prescribing decisions. I understand that the FDA's earlier draft guidance described a labeling approach that would include a statement regarding biosimilarity or interchangeability, yet the labeling for Zarxio does not identify it as biosimilar.

Dr. Woodcock, can you discuss how you are approaching the labeling guidance to ensure providers have easy access to the necessary safety information for prescribing decisions?

Answer 2. On March 31, 2016, FDA issued a draft guidance entitled *Labeling for Biosimilar Products*. As described in the draft guidance, FDA recommends that the biosimilar product labeling incorporates relevant data and information from the FDA-approved product labeling for the reference product, including a description of the clinical data that supported the safety and effectiveness of an FDA-approved biological (reference) product. The draft guidance also recommends that biosimilar labeling should include additional data from a clinical study of the biosimilar product only when necessary for the safe and effective use of the product by a healthcare practitioner.

Additionally, the draft guidance recommends a "biosimilarity statement" be added to the beginning of the Highlights section of drug labeling that describes the relationship of the biosimilar product to the reference product.

Question 3. In addition to the regulatory approval requirements necessary for manufacturers to invest in the development of biosimilars, another major variable is government reimbursement for their use. 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.

How is the FDA communicating with CMS on these issues?

Answer 3. Though FDA does not have a role in Center for Medicare and Medicaid Services (CMS) reimbursement decisions, in conjunction with the Medicare Physician Fee Schedule for 2016 final rule, CMS and FDA are developing an approach to use subcodes, also known as coding modifiers, to facilitate pharmacovigilance for biosimilar products that share a billing code. FDA currently relies on billing data that uses CMS payment codes to conduct post-market surveillance of products.

Question 4. We have heard from stakeholders how important it remains for FDA to resolve unsettled questions about the biosimilar approval pathway to ensure that patients have access to safe and effective biosimilars. FDA noted in its response to the April letter signed by several HELP Committee members, that the Agency cannot provide a specific timeline for the release of any guidance.

Now that the draft guidance on naming has been released, do you have an update for the committee for when we can expect the additional guidances—on interchangeability, extrapolation, and labeling—to be released for comment? When can we expect them to be finalized?

Answer 4. FDA has published the following *final* guidances:

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.

⁷ <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm>.

- Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product.
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.
- Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following *draft* guidances since 2012:

- Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.
- Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act.
- Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009.
- Nonproprietary Naming for Biological Products.
- Labeling for Biosimilar Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above.

Upcoming guidances are expected to include:

- Considerations in Demonstrating Interchangeability to a Reference Product.
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity.

FDA is diligently working to issue guidance on issues that have been identified by FDA and stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide guidance and information to assist biological product developers—sponsors/companies—with bringing biosimilar and interchangeable products to market. FDA is continuing to clarify its approach to implementation of the BPCI Act so that sponsors know the Agency's expectations.

SENATOR KIRK

Question 1. 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?

Answer 1. 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.

SENATOR HATCH

Question 1. In contrast to generics, biosimilars are large, complex molecules that are not the "same", but are rather "similar" to their purported reference products. To ensure patient safety and pharmacovigilance, biologic products must be clearly identified through distinguishable nonproprietary naming. I note that World Health Organization experts, taking a similar view, are considering the adoption of a "biological qualifier" that could be used in conjunction with the International Nonproprietary Name (INN) to accomplish this function. There is clear value in ensuring consistency internationally in order to avoid proliferation of different systems and to enhance traceability. Moreover, it appears that the WHO proposal is aligned with the draft FDA Naming Guidance in that the INN would correspond to the "core name" while the biological qualifier (BQ) would correspond to the FDA's proposed "suffix".

What is the Administration doing to engage the relevant World Health Organization bodies to ensure adoption of distinguishable naming for biologics through a BQ as soon as possible?

Answer 1. FDA is an active participant and leader within global regulatory organizations, including engaging with the World Health Organization (WHO). We attend WHO's meetings and scientific conferences, including the International Pharmaceutical Regulators Forum (IPRF) convened by WHO's Biosimilar Working Group. The purpose of the IPRF Biosimilars Working Group is to discuss issues and challenges associated with regulation of biosimilars in the member countries and promote scientific alignment where possible. FDA also has representation on the INN Programme, which convenes at several points throughout the year to discuss

and decide on various nonproprietary naming matters for drug and biological products, including the BQ proposal.

The draft guidance on Nonproprietary Naming of Biological Products proposes that originator biological products and biosimilar products have nonproprietary names (also called proper names) that share a core drug substance name and, in order to better identify each product, an FDA-designated suffix that is attached to the core name with a hyphen. This distinguishing suffix would be composed of four lowercase letters and devoid of meaning. The core name together with the suffix would be the nonproprietary name designated by FDA for the biological product (i.e., the proper name).

In contrast, in the WHO BQ proposal, the BQ would not be attached to, or considered part, of the international nonproprietary name (INN). In addition, the latest WHO BQ proposal states that the format would be four random consonants in 2 two-letter blocks (example, bxsh) with an optional two-digit checksum (08). Examples would be bxsh; bxsh08, bx08sh. The WHO proposal is voluntary; it would be up to the individual national regulatory authorities on whether and how to implement the BQ proposal.

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 is carefully considering all comments that have been submitted to the public docket.

Question 2. What is the Administration doing to ensure that the BQ or other distinguishable naming paradigm that may be adopted by WHO would be consistent with and implemented through the proposed Naming Guidance?

Answer 2. FDA is working closely with WHO to understand the technical aspects of its proposed naming policy. There are similarities and differences between FDA's proposed naming convention and the WHO proposal to assign a four-letter BQ to each biological substance to complement its 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 will carefully consider all comments that have been submitted to the public docket.

SENATOR CASSIDY

Question 1. Is it possible that FDA might approve an interchangeable product without first issuing guidance on interchangeability?

Answer 1. 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.

Question 2. Is there anything Congress can do to help FDA speed up issuing the guidance?

Answer 2. FDA is diligently working to issue guidance on issues that have been identified by FDA and stakeholders as key topics of interest, including interchangeability.

Question 3. 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?

Answer 3. 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.

Question 4. 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 with that 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 adequate to assure patient safety?

Answer 4. 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, MD. 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.

Question 5. 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?

Answer 5. 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.

Question 6. Can the agency comment on whether the concept of finger-print like similarity at the analytical level is linked to interchangeability requirements?

Answer 6. 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.

Question 7. 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.

Answer 7. 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 and a shift in priorities could influence these estimates.

Question 8. 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?

Answer 8. 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.

Question 9. Does FDA believe that biosimilars have the potential to be different enough from the reference product to require a different label?

Answer 9. 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.

Question 10. 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?

Answer 10. 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.

Question 11. 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 on the label?

Answer 11. 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.

Question 12. In 2012, FDA issued a Draft Guidance⁸ 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?

Answer 12. 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 guidance⁹ 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."

Question 13. The complexity and uniqueness of each biologic medicine require that FDA ensure that all biologics and biosimilars are thoroughly tested and meet the

⁸Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

⁹"Scientific Consideration in Demonstrating Biosimilarity to a Reference Product," <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

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?

Answer 13. 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.

Question 14. 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?

Answer 14. 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 are developing an approach to use subcodes, also known as coding modifiers, to facilitate pharmacovigilance for biosimilar products that share a billing code. FDA currently relies on billing data that uses CMS payment codes to conduct post-market surveillance of products.

Question 15. 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 guidance. Is FDA communicating with CMS on these issues?

Answer 15. As stated above, FDA does not have a role in CMS reimbursement decisions. We are working together on pharmacovigilance.

Question 16. 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?

Answer 16. 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 Biologicals Price Competition and Innovation Act of 2009."

Question 17. What is the FDA's stance on using post marketing data from countries like India for approval of biosimilars in the United States?

Answer 17. In order for a product to be licensed as a biosimilar in the United States, 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 United States is already approved outside the United States, 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.

Question 18. 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.

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?

Answer 18. 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).

Question 19. 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?

Answer 19. 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.

Question 20. Is the FDA concerned about the threat of improperly listed patents? As part of the 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?

Answer 20. 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.

[Whereupon, at 10:59 a.m., the hearing was adjourned.]

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