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BIOSIMILARS IN THE UNITED STATES: IMPLEMENTATION CHALLENGES AND LESSONS LEARNED FROM THE EUROPEAN UNION

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P R O C E E D I N G S

MR. WEST: Good morning. I'm Darrell West, vice president of Governance Studies and director of the Center for Technology Innovation here at the Brookings Institution. And we'd like to welcome you to this forum on biosimilars. And we especially appreciate you braving those torrential rains and the possible tornado warnings that are out there. I knew there was going to be trouble when I woke up this morning and my cats were upset because the windows were rattling so much, but we appreciate you coming out.

For those of you who are unfamiliar with the term "biosimilars," they are drugs that are similar to, but not identical to, innovator biologics. Unlike generic drugs, which could be determined to represent exact duplicates, biosimilars are more complex substances, and, therefore, raise interesting questions both for public policy as well as regulation.

In March of this year, Congress passed legislation designed to encourage biologics, price competition and innovation, and, among other things, this bill gave the Food and Drug Administration the authority to establish scientific standards for the approval of biosimilars, and it also authorized the FDA to determine the analytical and clinical data needed to assure patient safety.

Today we have brought together several experts to offer their views of the implementation challenges. Several other places, including the European Union, Canada and Japan have developed a pathway to approval for biosimilars. The European Medicines Agency, for example, already has established a process that is science driven and included the input of major stakeholders. Among the questions facing the FDA are how to identify and monitor adverse events, what kinds of clinical data are required for

approval, and how to involve the various relevant stakeholders in these decisions.

To help us better understand these issues, we are pleased to welcome three distinguished speakers, and they're going to focus on the regulatory and implementation challenges and opportunities, as well as comparative analysis of the European Union and Canadian experiences in creating a biosimilars approval pathway.

Anthony Ridgway is a senior regulatory scientist at Health Canada. In that position, he works at the Center for Evaluation of Radial Pharmaceuticals and Biotherapeutics in the Biologics and Genetic Therapies Directorate. He will tell us how Canada handles these issues and also will draw some comparisons with the European Union.

Mary Pendergast is president of Pendergast Consulting. She provides strategic and tactical advise to biotech and pharmaceutical corporations, governments, professional and patient groups and institutions on regulatory issues relating to compliance and drug development. Ms. Pendergast has served as deputy commissioner and senior advisor to the commissioner at the Food and Drug Administration. That was from 1990 through 1998. And then earlier she served as associate chief counsel for enforcement at the FDA.

Henry Grabowski is professor of economics and director of the program in pharmaceuticals at Health Economics at Duke University. He has published numerous studies on the pharmaceutical industry, with a focus on the economics of innovation, business regulation and industrial organization. He has served as an advisor to the National Academy of Sciences, the Institute of Medicine, the Federal Trade Commission, the General Accounting Office, and the Office of Technology Assessment.

Our format this morning is as follows: Anthony will start with an overview

of biosimilars and talk to us a little bit about his experience in Canada, and then following that we will hear from Mary and Henry. So, Anthony, we will start with you.

MR. RIDGWAY: All right, thank you. So I'm tasked with just giving you a bit of some of the background to the development of the Canadian guidance and perhaps some of the bumps along the way and some of the significance issues or concerns that were expressed.

And we have been thinking about this issue for quite a long time. I actually gave a talk at a conference in Strasburg in 1999, which was entitled "The Biologics Beyond 2000," and I was there giving a talk on comparability, the issue of when a manufacturer and innovator is making a manufacturing change and how you compare the version from the revised process to the earlier process.

But at the end of that talk, I did discuss the possibility of what we were calling at the time subsequent entry biologics. What's interesting for a conference that was called "Biologics Beyond 2000," it was the only talk that discussed this issue of what were to become known as biosimilars. We didn't do much for a while. We kind of -- we had an outlined document that we released to Canadian industry, that's been available since '99, and then we realized we should get moving because the European Union was making great strides.

We put a fact sheet on our website back in July, 2006, and from that point on, we started to work a little harder to develop a clearly described regulatory approach to what we call subsequent entry biologics and to develop appropriate scientific and clinical guidance.

And so there were successive drafts of the guidance document, there was an external consultation workshop that was held in May of 2008, and our final

guidance document was released in March, earlier this year. It's entitled "Guidance for Sponsors, Information and Submission Requirements for Subsequent Entry Biologics." And I wanted to give you a little bit about the motivation for doing this guidance document, and that is that it was not driven by political measures or the concerns about health care costs. It was something that originated internally within the Biologics and Genetic Therapies Directorate, and it started because it was obvious that copies of these innovative biologics were going to be coming along and that we needed to decide on what would be sufficient evidence of quality safety and efficacy.

There have been many years of safe real-world experience for some of these similar products and that must have some value. So in Canada, to date, for example, some of these products have been on the market for 20 to 27 years and used in millions of patients.

It's also true that there are multiple innovative versions of some biologics, all of which have been shown to be safe and effective, none of them of which are identical to each other, and, therefore, some differences clearly are not critical. And also, innovators make manufacturing changes usually with minimal or no clinical data. So all these things had to be captured and because practical considerations in our development of the guidance document.

And we felt we didn't really have scientific or regulatory grounds for refusing to evaluate a submission if it came in. Our regulations which focus on sufficient evidence of quality, safety and efficacy basically gave us room to evaluate these products. So as I said, it was internally initiated and wasn't politically or financially motivated. And as we worked, then others had to adapt. So there were corresponding changes to our guidance on data protection and post notice of compliance regulations.

Notice of compliance is what we give to a company when they have permission to sell the products, it's an approval.

But, of course, we were well behind the European Union when it came to this.

We used as a model for our guidance the comparability exercise which is undertaken by innovators after a manufacturing change. And we, of course, have a lot of experience with this, as do other major regulators.

We felt the need to incorporate the need for new clinical data generated with the subsequent entry biologic, and therefore, the data bridged through the demonstration of similarity is considered supportive. And we adapted international guidance, especially ICH -- International Conference on Harmonization -- guidance, and especially ICH Q5E, which deals with comparability.

I think our quality guidance document may be slightly more detailed than the EMEA guidance, which is high level. Our clinical guidance is written at a high level and is similar to the high level EMEA guidance. Unfortunately, we haven't had the chance to interact or collaborate with U.S. FDA colleagues. Not directly, but both Canada and the U.S. were involved in helping the WHO with their guidance document, so there was some interaction at that level at least.

So what's covered by the Canadian guidance? It's a comprehensive guidance in terms of what it covers, if not at least in detail. So there are general policy statements, we address various concepts and definitions, discuss the scope of eligible products, and there's cross-referencing in there to the regulations and guidances covering patented medicines and data protection.

There are considerations for selecting the reference biologic to be used as the comparator. The bulk of the information, of course, deals with what should be

provided in conducting the comparability studies for quality, non-clinical and clinical, and, therefore, to support a potential determination of similarity, there's information on what should go into the product labeling and also on post market requirements.

Again, our approach is guidance based. We have not yet made any regulatory changes specific to the pathway for evaluating subsequent entry biologics. We may eventually develop some product class specific clinical guidelines, but then we don't necessarily want to redo all the work that the European Union has done, and so currently we are quite comfortable with companies referencing and using the EMEA guidance documents.

So in our situation in Canada, these products are examined on a case by case basis. Full chemistry and manufacturing data is required, plus the comparability study with the referenced biologic. Clinical data is required. The amount of that data is negotiable and is influenced by several factors. And one should use the same reference product throughout the development of the program.

In our view, data supporting one indication will not automatically support all indications. However, if the same mechanism of action is used, then it may be possible to bridge those other indications with a rationale. If it's not known how the product is working or there are distinct modalities, different ways of acting, then additional data would be required for the additional indication.

And we believe strongly that these products should be thought of as stand alone products. Once they're on the market, these products, if they make a manufacturing change, will compare themselves to the earlier version of their own product, they'll no longer be asked to make comparisons to the reference product. And so that has implications over time with respect to substitution and interchange and

perhaps there will be more discussion of that later in the morning.

Some important clinical elements, the guidance is general, we don't have the same specific guidance on product class that the European Union has, for example. Comparative studies are required. Trials designed to show equivalence are strongly preferred, but not absolutely required. There may be ways to get away with a non-inferiority study, but if clinically meaningful superiority is identified, then the product can no longer be approved as a subsequent entry biologic.

The clinical indications that are being sought can only include those that are held by the reference or a similar reference biologic in Canada. And completely new indications not held by the reference product are possible, but then they would have to be supported by full clinical studies, and, of course, we want post-market vigilance and risk management plans.

Some closing comments, I don't know how I'm doing for time. Many years ago, when I was first talking on this product -- on this issue, it was quite significant to see how polarized the feelings were on the biosimilars or generics manufacturers and the innovative manufacturers. The biosimilars manufacturing say, oh, yes, we can do this, if you just treat them like chemical generics, and the innovators saying it's impossible, you can never make a copy of a biologic drug. The answer was always somewhere in between, and it's been comforting to see that both sides now I think have come together in the middle.

The European Union, in their approach, I think started out from the generics perspective and moved towards a stand along biologic. On the Canadian side, we started with a new drug submission approach and said, okay, what concessions, what relaxations can be made. And I think it's interesting that both the European Union and

Canada have ended up around the same place, even though we perhaps approached it from different directions.

One of the major elements of the Canadian guidelines that's raised a lot of discussion is the fact that we have said that under certain circumstances we would accept a non-Canadian referenced biologic, and there are significant reasons for that and implications for that, and that may come up for further discussion later.

So I think I probably had more than my seven minutes and I'll stop there, but I'm more than willing to discuss some of the other items that I hinted at in my opening remarks. Thank you.

MR. WEST: Thank you. Actually, it was a good seven minutes, so that's fine. Mary, you have extensive experience at the FDA, so I was wondering if you could give us a brief overview of some of the implementation issues and challenges before the Food and Drug Administration.

MS. PENDERGAST: I'd be happy to. But first I'd like to say, should we envy our Canadian neighbors to the north, where this was not either politically nor economically motivated? I think the one thing you can say about the United States is that the biosimilar legislation was definitely economically motivated, and there certainly has been enough politics in it for everyone to have a share.

So talking about the implementation of biosimilars, I was at the FDA, worked on the Hatch-Waxman legislation before it was passed, and then helped implement it. I litigated the first case under that legislation and have watched it over the last 26 years. And one of the things I would like to point out is that 26 years later, there are still court cases, there are still guidance documents coming out, there are still areas of that law that we don't understand or where courts have taken contrary positions. So if

you have a seminar next year at this time, do not expect everything to be decided, because it won't have been.

The one thing we do know is that the FDA has the power and it believes it has the capability of actually making decisions on biosimilar applications in advance of the FDA saying anything publicly about what its standards would be or issuing any guidance documents. So you never know what will happen in "real life" with respect to real applications.

But let me focus a little bit on some of the implementation challenges. And I would like to say that I did an assessment of how long it took us to do the guidance documents and regulations around Hatch-Waxman, and the first final guidance document did not happen for 12 years. Now, hopefully this will not be the case with biosimilars, but do expect a long haul.

So what are the big challenges for the FDA? I think the first challenge when implementing a piece of legislation that is a balancing act, and basically you're balancing money against safety and efficacy, you're trying to have cheaper products, which means you can't go to the very specific safety and efficacy questions that you would have with a pioneer drug, the question is, where will the FDA place itself on that continuum and how will it hold steady both within the FDA and over time taking that position? That is very, very hard to do. It will be especially hard to do when the decisions that are being made are being made by the Office of New Drugs, which means that there are 16 different review divisions that will be making the decisions on individual applications.

As we know from regular chemical drugs or from biologics that are being approved under BLAs, there are differences within those reviewing divisions. They have

different attitudes; they take different positions on different topics. I don't imagine this will be any different, and I think that will be a major challenge.

I think secondly, it will be difficult for the FDA to balance itself when we know that the politics and the attitudes of people are not going to disappear. Members of Congress have already told the FDA what they think the FDA should do which may or may not be identical to the law as is written. The FDA will be under pressure from both the innovator and the biosimilar industries to shade their interpretation one way or the other. Again, this is very, very difficult to the FDA.

So we also know from -- if you actually read the approvals for generic drugs, you know that it is very hard to get it right and it's very hard to get it right and consistent over time. So this is I think the FDA's first challenge.

The second great challenge I think that the FDA has, and I'm not sure it recognizes that it has, is that the FDA is being asked to make very tough scientific decisions, like is one drug biosimilar to a second drug, to an innovator drug. It's then asked to make an even more tough decision, which is, is the biosimilar drug -- can it be substituted for the innovator drug? Is there interchangeability?

Those are going to be tough decisions by the FDA, but what's going to be even harder is to get the FDA to cause the rest of the world to listen to them and obey those structures in the real world. And I think we have seen so far that there is very little enthusiasm on the part of payers, on the part of P&T committees, and on the part of others to actually decide to follow what the FDA is going to say. And so I think the FDA has some abilities to cause people to be as limiting in their decisions as the FDA would want them to be, but I think that the FDA has to decide it's going to care and then it's going to have to take action to cause the insurers, the payers, the P&T committees to

actually follow the scientific standards that the FDA has laid down.

And there's interesting things that the FDA could do with, for example, the contraindication section of the label, or having people get into trouble for causing the adulteration and misbranding of drugs. But the FDA, first of all, has to care, and I don't know if they do.

I think that the third major challenge that the FDA is going to have is going to be in pharmacovigilance. Now, we all know that we won't know very much about biosimilars before they're put on the market. There are some instances, including, for example, the Canadian guidance document, there's some suggestion from the FDA's Loginox decision, though the principal decision-making is going to be based on pharmacodynamic endpoints in healthy volunteers; that the clinical trials will be small, they'll be used biomarkers, sometimes they can be gotten rid of all together. So we know whenever the FDA is approving a pioneer drug, we know that we don't know it. The general rule of thumb when I was at the FDA is, avoid a drug for the first two years, let's see what happens in real life. That same thing will be true for biosimilars, perhaps even more so.

So the question is then how do you figure out through post marketing activities and through pharmacovigilance what the true make-up of a biosimilar will be over time? The problem is, we have a perfectly lousy pharmacovigilance system right now in the United States, everyone knows that, and it's rough, it's crude. A small proportion of doctors filed adverse event reports. The ones that do rarely fill out enough information that it's actionable by the FDA.

Sentinel is going to be -- shows promise, but it's not up and running yet. We don't have electronic medical records, and there is no one place. Even if the FDA

said someone must keep track of not only the name of the drug, let's say we have a world where each biosimilar has a particular name, a different name, a different INN, the lot number must be recorded on the patient's record, there's still no system where all the patient's records will get to the same place at the same time. So asserting our signals or problems, whether it's with a biosimilar or with a pioneer, is going to be incredibly difficult. And I think that there's not a lot the FDA can do about that at this point, they can't refuse to approve biosimilars until we have a decent pharmacovigilance system in the country, that won't work, but what can we do and how can we improve the vigilance system to take on this new challenge?

I think they should do whatever they can do, and I think everybody should, again, be doing everything they can do, because this is going to be a major challenge.

The fourth major thing, and I think the most difficult scientifically, is going to be -- or with policy is how to deal with drift. I think that the -- is no real sense of what we're going to do about this.

Assume for purposes of argument that you have a pioneer drug and it would stay exactly the same over time. Then the law that says you may file your application in year four for a biosimilar, so you're measuring yourself against the pioneer as it was in year three or year four, and you don't then get approval as a biosimilar to that innovator until year 12. Well, if the innovator drug stayed exactly the same over those 12 years, then fine, then the decision that the biosimilar is biosimilar to the innovator at year 12 will be true in some kind of scientific sense, but that is not the case.

Almost every innovator, certainly everyone I've talked to, changes their product over time. They change it for a variety of reasons. One, they change it to

increase yield, that is to say to make more money off of their investment. Second, FDA requires changes. We forget about this, but it's certainly true. They say to innovators, narrow your release limit, get rid of that impurity, do this, do that, so the pioneers are also changing over time.

If you have a pioneer in year 12 that has a product that is different from the drug, the biologic that was tested for the biosimilar at year two or three, at year 12 are they going to be biosimilar or not? And how do you deal with that and what do you say, and how do you measure it? There won't be, unless the FDA compels it, a second look at biosimilarity at year 11 or year 12. So this I think is going to be an interesting thing.

Secondly, what you do is assume two things are biosimilar, the innovator and the biosimilar, and then over time, each of them changes. We saw this certainly with Amgen and J&J's versions of EPO, where they started at the same, and then, for a variety of reasons, they drifted over time away from each other. What do you do about that? What do you do about -- similar companies have said FDA must compel the innovator to never change the innovator, right, well, I can't imagine that that is going to be an acceptable standard.

So assuming that an innovator gets to keep changing, what do we do about this and how do we handle it? Same with interchangeability; is interchangeability going to work for a long time, or is interchangeability going to have to be reassessed over time depending on the drift?

And I don't know the answer to these questions, but I do think that it's a little too simplistic to say, well, innovators change their product over time and they don't do clinical trials, so obviously, 12 years later, they're going to be the same. The fact of the matter is, they do change their product and they do do clinical trials to measure those

products. And there are changes, and we've seen that with Genzyme, where the changes get so great that the FDA requires the company to submit a separate BLA and to call it a different product.

So what are the decision points? What are the decisional rules? When does FDA decide it's a new product? When does FDA consider it in the linear fashion of the innovator? And when does a biosimilar change drift over time such that it's no longer biosimilar?

I think that this is an incredibly challenging thing. I do not have the answer, but if I was going to be watching something that I think will change over time and will be very interesting, that's the place I would look. So I will stop there, save time for questions.

MR. WEST: Okay. Thank you very much, Mary, for providing that overview. Henry, you are an economist at Duke. Tell us about the economics of biosimilars.

MR. GRABOWSKI: Okay. So this legislation, as many of you know, took several years in the making. And I think when legislators started; they sort of had the generic model in mind. And they thought, well, if we pass a law, that we will get this kind of rapid and deep price competition that we used as a cornerstone of cost savings for pharmaceuticals. But over time there was the realization that it's not going to be just like chemical generics, that biologics are these large complex molecules from cell cultures that likely there will be, as we've heard, some requirement for clinical testing that's for safety and efficacy. That's true in the EU and it will probably be true in the U.S., certainly for the most complex biologic.

And that means that rather than an entry cost in small molecules of a few

million dollars, we're talking about tens of millions of dollars to do some pre-clinical and clinical testing. And the upshot will be, there will be fewer entrants, and the entrants will be focused on the very largest selling products.

The other issue that's important for small molecules is substitutability, interchangeability. In the law it says that if a product is to be administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the products is not greater than the risk of using the reference product alone for any given patient. So how does the FDA determine whether a product is interchangeable?

Some regulatory experts, including ex-FDA, say the way you're going to have to do that is with crossover studies, where patients start on the reference product and then they're shifted over to the biosimilar, and one looks at this results over time and across these groups. And those kinds of studies are very expensive; they're difficult to recruit patients. As a result, many biosimilars may choose not to be interchangeable, but to be therapeutic alternatives.

So how does that shape up economically? I think the interchangeability may not be as critical as was thought because most of these products are not the kind where you take a script to a drug store and they can substitute or not. They're dispensed within hospitals or clinics. And the critical actor is going to be the P&T committee to determine whether these -- that they're comfortable, that these products, particular for new patients, are therapeutic alternatives of high quality, and then there will be lots of economic incentives, associated with that.

And we also have lessons from Europe. Germany is the kind of leading edge of usage of biosimilars, and basically they have had biosimilars for erythropoeitin

now for two years and for the G-CSF's products like Neupogen for one year. And the penetration against the reference product, Eprex in the EPO area is now at 60 percent. We're seeing price changes. The price discounting of the biosimilar relevant to the reference product, that introduction is now around 40 percent. And we also see the reference product dropping its price, not the full 40 percent, but a significant amount, part of the way towards the biosimilar in Europe, and that's all without any kind of substitution or interchangeability.

And in the kind of U.S. situation, we have a mosaic of different payers here, but, you know, at one end is hospitals, where a lot of these products are dispensed. And they're very cost-sensitive because they have global budgets, the so-called diagnostically related group budgeting, where a drug is bundled with other services. And to the extent they're comfortable with a product as a good therapeutic alternative that's cheaper; they have strong economic incentives to use it.

We also have a lot of these products reimbursed under Medicare Part B, that is dispensed say for oncology and a physician's -- an outpatient clinic, and they're reimbursed the average selling price plus 6 percent, the providers. They're buy and build kind of: they buy the product, dispense it, and then are reimbursed by HHS for the selling price, the average selling price.

Now, there was a concern that if the biosimilars were cheaper, you'd get -- the provider's margin of 6 percent would be not a good incentive to use the cheaper product. So what Congress did in the law is to say that provision -- basically the reimbursement is AST for a biosimilar plus 6 percent of the reference drugs AST, so that the 6 percent margin amounts to the same amount of dollars.

And then one can look to HHS to involve other kinds of incentives to use

in the coverage, decisions to use these products assuming they are viewed as therapeutic alternatives. Once again, the P&T committee will have a large say.

Now, there are products that are self-injectables, products, for instance, MS, or human growth hormone, or various other products, and they're reimbursed under Medicare Part D, which is where our old drugs are reimbursed. But many of those Part D plans have a tier 4 co-insurance rate of 25 percent or more.

So to the extent that the biosimilars are cheaper, there will be strong incentives to utilize them if they offer significant discounts and if they are viewed as good options, even if they're not interchangeable. And managed care historically has focused more on, in the private sector, on oral pharmaceuticals. But given that the patient populations are smaller, one can expect to -- they could utilize instruments like step therapy, prior authorization and others, as well as formulary tiers.

And as I said earlier, I think where this will be -- particularly if the products are not interchangeable, then it will be -- the usage will be -- particularly the penetration will be greater where the patient population turns over more rapidly, like for neutropenia or in some of the oncology areas. You'd expect lots of new patients over time, and that's where the biosimilars might be more utilized.

For areas where there's chronic long-term diseases, you know, some rheumatoid arthritis, where patients are already well treated on an existing product, it may be slower penetration.

So I was also asked to talk a little bit about the data exclusivity part of the law. Basically, Congress had to balance keeping incentives for biologic innovation with incentives for, you know, an abbreviated pathway. And I think it's important to maintain incentives for innovation because biologics are where a lot of our novel and first in class

drugs are appearing, particularly in areas like oncology. Right now about half the drugs in the clinic are biologics in clinical trial settings, and they are very rapidly growing. And many biologics have systematic effects, so that the TNF inhibitors not only are for rheumatoid arthritis, but for other autoimmune diseases like psoriasis and Crohn's disease. Many of the biologics for oncology are useful not only just for one area of oncology, but for several, so it's important to have a long enough period after initial introduction to explore multiple indications.

And the data exclusivity, people say, well, if we have patents, why do we need some period before the data exclusivity, it's the period before a biosimilar can rely on some of the initial safety and efficacy data to get an abbreviated approval.

Congress eventually settled on 12 years after a lot of debate, should it be 5 years? Should it be 14? Some say we don't need it. I think the reason you need some kind of exclusivity is often the drug candidates, the good drug candidates, good therapeutic candidates may not have good patent protection. It may take a long time so that the core patent time is eroded.

It may be that one could get around some of the patents without infringing. And in the biological area, many of the patents are formulation patents and process patents. If a biosimilar uses a different process, maybe it's non-infringing. So I think there was a concern that the products may be similar enough to get an abbreviated pathway, but different enough not to violate the intellectual property in patent.

So there was a period -- a data exclusivity period of a significant amount put into the law. I did some economic analysis on how long does a representative biological typically take to kind of pay back the large R&D cost, as well as earn a competitive rate of return, and I got numbers in the 12- to 14-year basis. And I think this

is also consistent with Europe, which has 10 years plus an additional year for new indications. In the U.S., we have 12 years, but many anti-evergreening provisions that we can talk about if we have time.

So basically and sort of to conclude, I think there's lots of basis for cost savings. We tried to look at when the top 20 biologic products could be subject to biosimilarity in an emerging paper to biosimilar products, and we found that, first of all, there's a highly skewed distribution. The top 20 biologic products account for more than 60 percent of current sales, and most of these products begin experiencing patent expiration and the end of their 12-year data exclusivity period starting in 2012. In 2013, there's a huge jump, more than $10 billion in products, including some of the NIT&S, some of the monoclonal antibodies, EPO, Epogen and Procrit, Neupogen and so on, so that by the years 2015, many of the leading products would be available for biosimilar substitutions.

So I think there's lots of opportunities here, and particularly if the regulators begin approving these products over this time frame.

MR. WEST: Okay, thank you very much, Henry. I will have a follow-up question for each of our panelists and then we'll open the floor to questions and comments from you. So we'll start with Anthony.

Both Mary and Henry mentioned substitution and interchangeability issues and how they will operate, and I'm just curious, what factors do you think regulatory agencies should consider in determining whether a proposed interchangeable biological product will produce the same clinical results? And how do other countries address this issue?

MR. RIDGWAY: Well, a good question. As Henry mentioned, there are

ways to show interchangeability: complicated trials; switching drugs back and forth, that can be complicated for biologics because they tend to last a fair amount of time in the body; and allowing for wash out periods between dosing may not be appropriate, it may not be ethical because the patient should be on the standard of care, so there are numerous challenges to try to clearly demonstrate that a product is interchangeable.

But I'd like to go back to some of my earlier comments and comments that Mary made to defend the Canadian federal opinion that these products should really be substituted. They could be interchanged with a physician's intervention.

I guess I should clarify, this issue of substitution interchange also depends on definitions, and the definitions vary in different parts of the world. So in some places substitution interchange means essentially the same thing. I think in the U.S. interchange would be what was meant by substitution in Europe and vice versa, so it's very complicated.

But if I start out by saying that automatic substitution would be where a country or a province or a state or a payer required that a drug be automatically substituted, so that would be automatic substitution. Substitution, general substitution would be where the pharmacist, without consulting the physician, made the switch, and then interchange, in my set of definitions, would be where the physician, either by themselves or after consultation with the pharmacist, the physician decided that it would be okay, hopefully in consultation with the patient as well, to switch a patient from one product to another.

Mary expounded on an area that I was going to get into, which is that this demonstration of similarity, and even interchangeability, if one went to the lengths of study to demonstrate that, to me, those are moments in time, we've captured moments in

time where it was shown to be true, a certain bar was met, but from that point on, you can't be sure.

And manufacturing drift is something real for biologics. As the innovator makes manufacturing changes, and they compare their product to the earlier version of their own product, and the biosimilar manufacturer does the same thing. If you were to compare the same products five years later, they may not meet the same bar of demonstration of similarity.

So if we know that, I think we need to be cautious about clearly saying that a product is substitutable or interchangeable. As I said in my opening comments, I think these products should be thought of as standalone products, that they get onto the market with a slightly different clinical data package than the innovator product, that data package, in Canada at least, will require independent studies with the biosimilar itself, direct head-to-head comparisons with the reference product. And then there's a whole mess of other data which is more or less valuable depending on the perspective of the reviewer and the agency, supportive data generated over time through the real-world use of the reference product, which gives some measure of confidence, if not to the regulator and the evaluator, then perhaps to the physicians who have been following the use of the drug for the previous 15 years, that there is safety and efficacy associated with the biosimilar to that reference product. So three kinds of data that all go to build towards it.

But once these products are on the market, I can't see a way that it would be feasible, economically practical to force the biosimilar manufacturer to do repeat comparisons to the innovator. And even if they did, if they miss the mark, then what are they going to do? They're going to tweak their manufacturing process again to try to follow whatever the innovator has done. It's just -- it's not conceivable.

So I think they have to be thought of as stand alone products, just the same as the five or six different versions of innovator growth hormones around the market. These products are all similar and different, to some extent. They're not necessarily used interchangeably, but physicians would have confidence in some instances switching a patient from one version over to another, and I think that's how one should think of biosimilars.

In Canada, it's our provinces and territories that make the determination as to whether or not a product should be substituted or can be substituted or not, it's not the federal government's jurisdiction. But we've been engaging in discussions with the provinces and territories to try to get across our message that we should -- that these should be thought of as standalone products. And I think it's telling that in Europe, most of the countries in Europe have laws against automatic substitution, as I defined it earlier. And many of them also do not allow substitution by a pharmacist, although I think everyone appreciates the idea that if a physician decides to switch a patient over, that they're allowed to do that under the practice of medicine, and I think that's the route it should be done.

MR. WEST: Okay, thank you. Mary, several manufacturers of biosimilars sold in Europe have suggested that they will not use the new abbreviated approval pathway in the United States; instead they will submit a full BLA application for attempted copies of biologic medicines rather than use the biosimilars approach. What are your thoughts on how companies will react, and how should the FDA consider such applications if that is how it turns out to be?

MS. PENDERGAST: I think that the question of whether or not biosimilar companies should use a "skinny BLA," that is to say an application filed under

Section 351(a) of the Public Health Service Act, which requires the full safety period and potency requirements, where there are no attendant obligations on the part of the company to deal with the patent provisions of the biosimilar law.

When those companies say that we want to use a skinny BLA under 351(a), whether they're saying that because they think that the FDA scientific requirements for biosimilarity are going to be too strenuous, or whether, and this is my guess, that what they're really saying is, we don't like the patent provisions that are associated with biosimilars and we want to get around or duck those patent obligations by filing a straight BLA under 351(a) rather than a BLA-K under the biosimilar provisions of 351(k).

The reason why I say that is that the patent provisions, the biosimilars, as I understand it, did not receive very much attention at all in the heated debates about biosimilarity. Most of the challenges to and fro with the negotiators were over the scientific standards. And I think when the law was passed and the dust had settled, there were a lot of people sort of disappointed at how the patent provisions are written.

But be that as it may, I know that people want to file full BLAs, or really partial BLAs under the guise of a full BLA. I think that -- I haven't decided -- I was studying this myself over the past several days, whether or not I think the law permits someone to file a skinny BLA under A or whether or not the law as it is written really compels them to file a BLA under Section K.

And I think that that's what Congress intended. Whether Congress used the right words or not is a matter of some debate. I'm inclined to think that you really shouldn't be able to have your cake and eat it, too. In other words, get to use the innovator's data without the corresponding obligation to the innovator pertaining to the

patent laws that just seems to violate the spirit of the law, which was a give and take, and everybody got something, nobody got everything.

So we will see: the courts will ultimately make this decision. I think the more sensible interpretation of the law is that if you're intending to use an innovator's data without a right of reference, then you should be filing a BLA-K.

MR. WEST: Henry, I have a cost savings question for you and then we'll open the floor to any questions and comments from the audience. I mean, it seems to be that people do expect there to be some cost savings from biosimilars. But then when we kind of look back at the Hatch-Waxman experience in the 1980s, and then after that, the growing consumer preference for generic pharmaceuticals, when we look ahead on the biosimilars issue, do we expect the same type of dynamic to take place, that over time consumers will feel more comfortable, physicians will feel more comfortable, the market will expand, and then we will see cost savings?

MR. GRABOWSKI: Yeah, I think there will be a dynamic. I mean, even if you go back to 1984, it took almost a decade before the cost savings became that dramatic for generics. And now generic drugs and small molecules are two-thirds of all prescriptions.

I don't think we'll see that dynamic in a short timeframe. I think the issue is, how long will it take? But I think we'll see, you know, for some of the big selling biologics, even if you get three or four competitors, which you're likely to get for erythropoeitin and some of these other drugs, there will be a significant cost savings. You know, maybe prices will go down 30 percent rather than 80 percent that you get low-cost entry in chemicals, but 30 percent of the several billion dollar drug is real.

I was on a panel with a CalPERS person, and Congressman Waxman

asked them that. He said, you know, Professor Grabowski says it's only going to go down 30 percent, is that real savings to you? And said that's a lot of money in California. So I think that's the kind of -- it will be slower, but it will be meaningful.

MR. WEST: Okay, thank you. Let's open the floor to any questions or comments that you have. We have a microphone, so if you can raise your hand. We have a question up front, so if we can bring the microphone up. And if you can give us your name, your organization, and we'd ask that you keep your question brief just so we can get to as many people as possible.

MR. BOR: Jonathan Bor. Can you hear me?

MR. WEST: Yes.

MR. BOR: Of Internal Health Affairs. I know you've all touched on this, but I'm a bit confused about this question. In Europe, Canada and the U.S., to what extent will makers of biosimilars be required to conduct full-blown clinical trials to show safety and efficacy versus being able to rely on the innovator's own data?

And I know that has to do with data exclusivity, but let's say that period has expired. Can you just -- if you've shown chemical biosimilarity, can you just rely on the innovator's trials or do you have to do anything to show that your own product meets the passage?

MR. WEST: Good question.

MS. PENDERGAST: Do you want to go first?

MR. RIDGWAY: Well, in Canada, we have said clearly that we expect clinical data generated with the subsequent biologic. So I don't know whether we would be interested in going back to look at the innovator's data in the files or whether that would be even legal. It is legal for us to do that for generics. I'm not sure that it is legal in

the current regulatory framework.

If we do introduce regulations in the future, as I said, right now our approach is guidance-based. If we do introduce regulations, regulations to allow us to clearly go back into the originator's files for that purpose, it's probably something we would look into drafting or developing.

But regardless of what actually -- well, I shouldn't say -- both the U.S. and Canada have said that they did not go into the innovator's files to make decisions with respect to Omnitrope, so the decisions on Omnitrope were made looking at the data that the sponsor, Sandoz, produced themselves with their own product and with the reference product that they purchased on the market and references to data in the public domain, which was no longer proprietary, which illustrated that the referenced product was safe and efficacious. So our expectation is that we will see the -- that we expect (inaudible) studies with the biosimilar, that there should be head-to-head comparative studies, and they would be the main part of the clinical package.

Now, I haven't been back and done this myself, but I've seen charts produced by others which suggest that the number of patients actually treated in the -- in gaining approval of Omnitrope or human growth hormone and looking at some of the other products, G-CSF, for example, that the number of patients actually used was not too different from what the innovator used for their first approval.

So I don't think that there's going to be a huge problem in terms of differences in the amount of clinical data available, I think that's going to change as we move up to the monoclonal antibodies, where some of the trials involve thousands of patients, and whether or not the biosimilar manufacturers will get up into those kinds of numbers for patients.

MS. PENDERGAST: I think that you have to be careful. There's really two kinds of clinical trials, clinical just means human. One set of clinical trials are the pharmacodynamic pharmacokinetic trials that are conducted. I don't think that there will be any biosimilars approved without those trials, so they're technically clinical. But I do think that there is going to be cases, as we saw with Loginox, which is considered a biologic in many parts of the world, where there will only be pharmacodynamic trials. And the clinical trials that reach safety and effectiveness endpoints will be required for a while, let's say the next five years. But as the analytical ability to characterize these proteins goes up, the requirements for clinical trials may go down, depending, of course, on what we see as we muddle through this for the next five or so years.

I also think that the clinical trials may not be the classic kind of clinical trials that we're used to seeing for innovator biologics in the sense that they will run all the way out to the end clinical endpoints. So if it's oncology, all the way out to overall survival. It may be that they will run out as far as pretty well-defined biomarkers, and then maybe get approval with an obligation to finish the trial post approval.

So it wouldn't surprise me if, over the next stretch, that we have products approved with pharmacodynamic information and clinical trials that are at least getting to the biomarker endpoints. But it's like if you look at the TNF inhibitors, there's four of them. The first one -- I won't get the numbers right, but the first one had to study 1,200 patients, the next company had to study 2,400 patients, the next had to study 4,800 patients, and the last one was like 14,000.

As the FDA learned more, it got more scared about what the problems were. It's sort of hard to picture them going from 14,000 to 0 like that. So I think there will be a transition.

MR. RIDGWAY: And just to add, when you hear the FDA, they seem most concerned about the kinds of issues for biologics more than other aspects.

MS. PENDERGAST: Yes, that's true.

MR. WEST: Other questions? Right there on the aisle near the back.

MR. LOSS: My name is Ira Loss. I'm with Washington Analysis. At the recent FDA hearing, there was considerable discussion about the naming of these products. Mary, do you think that FDA's decision last year on the Botox products, giving each of them a different name, is precedent setting for what's likely to come?

MS. PENDERGAST: Yes, I think it is. I think that if you look at the systems we have in this country for post marketing drug safety, the pharmacovigilance systems as they exist, I don't know how the FDA would be able to follow the safety of these products in our situation right now without different names.

We don't -- I mean, could you do it with bar codes? Yes. Do we have that system in place everywhere? No. So I think that, as a practical matter, I don't see how the FDA can get around making that requirement at this point.

MR. WEST: Other questions? Right here on the aisle.

MR. SHAW: Hi, my name is Timothy Shaw. I'm a postdoc at National Cancer Institute. I have a question particularly for Professor Grabowski regarding the potential implications for the approval of biosimilars to the business planning for the biologic innovators.

I can see at least they can do two things: one is to raise the price for the initial product, and the other is to kill other more promising drug candidate early in their path, and then society will lose more innovation that way. And could you comment on the implication that way? Thanks.

MR. GRABOWSKI: Well, in terms of raising price, which is more of a -- was a typical strategy for small molecules to kind of -- at least when they could retain some of the market to raise price to the most brand loyal customers, this is going to be a different kind of competition. If you only have three or four products that are somewhat standalone, that have different names, that are therapeutic alternatives, I think the likelihood is you lower price, at least to some of your most important customers, to kind of try to keep those customers. Maybe you don't price exactly like the biosimilars, but it will be a kind of different kind of -- it will be more like brand-to-brand competition.

In terms of killing products, I think the strategy might be to try to replace products, you know, with a new generation product. So, you know, by the time you get to one class, you have the next generation that has some therapeutic advantages relative to the earlier one.

And there's an interesting issue with data exclusivity. Congress says basically in these anti-evergreen greening provisions that you don't get a new data exclusivity period for a new formulation, a new indication, a new dosage form. That's all embodied in the original data exclusivity for the first product. But if you have a next generation product from the same manufacturer, they have to demonstrate some therapeutic advance in safety, efficacy or compliance to get a new 12-year data exclusivity. And the way I read the law, the FDA is going to make that decision, that it's -- the next generation warrants a 12-year data exclusivity.

So, you know, I think just thinking about the way companies would strategically behave, just like in the small molecules face, before the generics can take the market, you want to have the next generation product on. But I think then the payers will have to determine if this next generation product is really worth paying a higher price

for in terms of quality.

MR. WEST: In the very back, there's a hand up.

MR. SILK: Hello, my name is Eric Silk. I'm with Capital Street. Thank you for your panel today, it's been very informative. I don't know if this is proper or not, but I was wondering if Mary could comment on two applications that are pending in front of FDA and your thoughts on Teva's Neutroval application and the generic Lovenox?

MS. PENDERGAST: Okay, well, I don't work at the FDA anymore, and fortunately, they don't leak documents to me, so I have absolutely no inside information on either of those products. What we know from the public record is that the FDA did approve one generic copy of Lovenox. It has not yet approved -- it's public knowledge that there's other applicants, ANDA applicants whose applications are pending in front of the FDA.

There's controversy over whether -- or why they're not getting approved. There's lots of potential reasons why they're not getting approved. My guess is that since the raw ingredient for low molecular weight Heparin is still Heparin, and Heparin is sourced often from countries such as China that have had great challenges with good quality Heparin, properly manufactured, properly labeled, properly shipped, properly whatever, it could be that -- it could be, you know, a bad inspection, it could be an insufficient data package, it could be all sorts of things. So I have no inside information on what's going on.

MR. WEST: Yeah, we're good on policy advice, but not so much on market timing questions. I have a question. A couple of you have mentioned adverse events, and I'm just curious, how do you think we should monitor adverse events? And, Anthony, in Canada, how are you monitoring adverse events?

MR. RIDGWAY: Well, we have pharmacovigilance programs, and we are no better than the FDA. I think the world in general has problems, major issues around how to collect data on adverse events to support thorough pharmacovigilance.

But I did want to comment that I don't think the issues are anymore significant for biosimilars than they are for any other biologic product that's newly released onto the market. So I don't think there's anything particular to fear from biosimilars.

And pharmacovigilance programs and management plans, risk management plans, are becoming standard for all biologic products that are approved, and are not only introduced for biosimilars because of some perception that they may be less safe than other products.

I think that -- in Canada, we don't have class A and class B approvals, they don't do that in Europe, and they don't do that at the FDA. And I think U.S. citizens should have confidence in the FDA that the FDA will do a thorough job of evaluating these products and will not allow unsafe products onto the market. I think we've all benefited from the situation of the European Union being ahead of everyone else and that there are now multiple approvals in the U.S., in the EU. The EU regulatory system has allowed through the good ones and has denied or forced withdrawal of the ones that didn't meet the mark. Those products are getting widespread use and are being used in millions of patients, and so far there have been disasters that I'm aware of. So I think we can all benefit from the market experience that's being generated in the European Union.

It is very important to be able to identify products clearly, and, therefore, at Health Canada we have said that products have to have their own clearly identifiable name, and I think that's a wise decision.

I think early on, biosimilar manufacturers were thinking that perhaps, you know, it would be best to be prescribed by an I&N name so they could just sneak in the back door and not be recognized. But I think the feeling maybe has changed, that many of these companies that are going to great expense to develop these products want to maintain their own brand, and so we're going to kind of have branded biosimilars. They'll want the market to know that if there is a problem, it wasn't their problem -- their product that was causing the problem. So I think there's been a lot of noise and concern about the naming issue, but I think it'll all settle out and these products will have an identifiable name and that will contribute to whatever we can do with respect to collecting reasonable information on adverse events.

MR. WEST: In the very back, I think there's a hand up. Are there other questions?

MS. PENDERGAST: I'd just like to respond to that. No federal agency, no governmental agency is ever, ever going to put a product on the market that it thinks might have a safety problem. I mean, they'd be crazy to. But I think that we all know that there is always an unknown. We saw that with J&J's Eprex, where it caused red blood cell aplasia. We saw the same thing happen with one of the EPO biosimilars in Europe.

And so, you know, are there thousands of people dying in the street? No. Are there people that are blood transfusion dependent for the rest of their lives? Yes. So I think is -- I think what we all agree, I mean, that it's really important to be able to have a system that can figure these things out. And the problem is, we don't yet have a good system for doing that cheaply and effectively, but I think everybody does and should want it.

MR. WEST: Any last questions? Okay. We'll give you the last question,

right there.

MS. CRITTENDON: Hi, my name is Janna Crittendon. I run a firm in Boston and in D.C. here, it's JC Consulting Group, and I work almost exclusively in specialty pharmacy issues. My question, Mary, has to come to you, because I think you raised extraordinary issues that will not be easy for the FDA to solve.

My question would be, given how it is that the statutes dictate what the FDA can and cannot do, and many things that you have raised very well may be outside some of those current statutes, how would you expect the scientific integrity and the true nature of what these questions get to to be handled?

MR. WEST: A great closing question, although not an easy one.

MS. CRITTENDON: I'm a former journalist.

MR. WEST: Well, then we can hardly wait for the follow-up.

MS. PENDERGAST: I think the FDA will have to get out of its comfort zone and will have to not pretend to act as though the biosimilars law, although it says the Secretary -- and the Secretary of Health and Human Services has definitely, you know, given it to FDA, the FDA needs to look very broad, or maybe Brookings could help them look very broad and say who are all the players here that have to work in a coordinated fashion to make this law, whatever it says. However it is highly interpreted to mean work well in our health care system.

And so I think that the FDA's meeting that it held earlier this month, I give kudos to Rachael Berman and the people at the FDA. They had it as a very interactive meeting; they asked questions, they've got an open docket for everyone to respond to.

But if I were the FDA, I'd probably take it a step further. I would probably hold a meeting of all the insurance companies and say, what are you guys thinking. I'd

probably hold a meeting with the P&T committee saying, what are you guys thinking. I'd hold a meeting with CMS, what are you guys thinking, in other words, how are we going to make this work, because there's lots of different players, this is not just about the FDA at all.

So I think that that's going to be really hard and the FDA needs a lot of help on that, because it isn't what they're charged with doing. You know, they don't interact with P&T committees. They think -- they know it's not true, but they act as though -- they have to act as though if they put things on a label, people read it and listen to it and follow it.

When I was at the FDA, I was always thankful that there was the product liability and medical malpractice laws out there, because I knew that the FDA -- and that was back when our most severe penalty was a year in jail, but we couldn't actually make anybody do anything. We had to have coordinate laws that when we put out a standard, there were coordinate laws that actually made people do things.

And I think that that -- it's that kind of attitude that will have to be brought to bear on this law and these issues.

MR. WEST: Okay. I want to thank Mary and Anthony and Henry for sharing your views. Clearly, there are a lot of issues yet to be resolved here, but we will be following that. And thank you very much for coming out as well.

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