

FTC Follow-on Biologics Workshop
February 4, 2014
Segment 1
Transcript

ANDREW GAVIL: I ask everybody to please take your seats, and we will get started. Good morning, everyone, and welcome to the FTC's follow-on biologics workshop. My name is Andy Gavil and I'm the director of the Office of Policy Planning here at the Federal Trade Commission. We all appreciate the level of interest in the workshop and are very grateful that so many of you have joined us today, especially in light of our cancellation in December and rescheduling. We hope many others will also take advantage of today's proceedings by our webcast, and the record of today's proceedings will be on our website along with the webcast for future reference.

Before we get started, I need to review some administrative details and then ask for your patience. First, please turn off or silence any cell phones or other electronic devices that you have. Second, if you leave the building for any reason during the day, you will have to go back through security. Please keep that in mind in planning ahead, especially if you are participating on a panel so we can remain on schedule.

Please try to avoid having conversations out in the hallway directly outside the auditorium while panels are in session. The background noise from the hallway carries into this room and can sometimes disrupt the discussion. Also, the microphones that we're using for the webcast are very sensitive, so some of those hallway conversations may be picked up by the court reporters or the webcast. So if you do speak in the hallway, speak loudly so that everyone in the world can hear you.

Fourth, the restrooms are located out in the lobby behind the elevator banks and to the left of the security guard desk. Fifth, in the unlikely event of an emergency and the building alarms go off, please proceed calmly to the main exit in the lobby and assemble across the street on the sidewalk in front of the steps of the Georgetown Law School. The security guards will let us know when it's safe to return to the building.

I'd also like to remind all presenters and panelists to speak directly into the microphone so that everyone can hear your remarks and that we have a clear record of today's proceedings. And please, speakers, be attentive to our time keepers who will be right in front of the podium. Finally, if anyone has questions throughout the day, feel free to ask our staff. We are wearing FTC staff badges or those sitting at the registration desk, and we'll be happy to help you with anything that comes up.

To open today's workshop, it's my great pleasure to introduce FTC Chairwoman Edith Ramirez. The chairwoman has been especially interested in continuing the agency's longstanding commitment to promoting competition in the health care field, and we are really delighted to have her join us to open today's workshop. Chairwoman Ramirez.

[APPLAUSE]

EDITH RAMIREZ: Thank you, Andy. And good morning, everyone, and welcome to the FTC's workshop on follow-on biologic medicines. At the outset, I wanted to start by thanking the speakers who are joining us today and especially those of you who flew in back in December when we had to cancel the workshop due to the storm. And I also wanted to thank staff from our office of policy planning who have now organized this workshop twice. And including, in particular, Elizabeth Jex, Susan DeSanti, Erin Flynn, and Chris Ryan.

What I wanted to do this morning was just to take a couple of minutes to set the stage for today's discussion. As all of you know, biologic medicines are among the most important pharmaceutical products available today, providing lifesaving therapies for difficult to treat diseases such as cancer, diabetes, and multiple sclerosis. They're also among the most expensive, with costs often exceeding tens of thousands of dollars per year. Others have a price that is substantially higher, and these costs may prevent some patients from accessing potentially lifesaving therapies.

Introducing competition into the biologics marketplace represents one of the most promising ways to reduce prices and expand access to these critical drugs. Most consumers are familiar with the cost savings associated with the introduction of generic drugs to compete with traditional brand name drugs. The abbreviated FDA approval process, created by the Hatch-Waxman Act to introduce safe and effective generics, has spurred price competition and expanded consumer access to many widely prescribed small molecule drugs.

Recognizing the benefits of the Hatch-Waxman process, in 2010, Congress passed the Biologic Price Competition and Innovation Act, which created a statutory framework for follow-on biologic competition. This law required the FDA to develop an abbreviated approval pathway to promote competition for follow-on biologics, including both biosimilars and interchangeable biosimilars. While the FTC's 2009 follow-on biologics report found that a number of factors may result in different competitive dynamics in markets for follow-on biologics, it concluded that their introduction is likely to result in lower prices.

Of course, savings are less likely to be realized if there are regulatory or other hurdles in place that inhibit the development or adoption of follow-on biologics. Before businesses decide to invest millions of dollars in developing any new product, they assess the market to determine whether it's conducive to new product entry. One important factor that can affect entry is the regulatory landscape. Does the landscape facilitate new entry or create unwarranted obstacles?

Although the FDA has yet to approve any biosimilar drug, the evolution of that regulatory landscape beyond the FDA approval pathway already appears to be under way. Accordingly, the time is right to consider this future market, particularly since policy decisions being made today may have a crucial impact on how competition for biologics plays out in the years to come.

Well, it appears that, under federal law, an FDA approved interchangeable biosimilar may be substituted for a reference biologic without prior prescriber consent, there is substantial uncertainty, at the state level, surrounding how follow-on biologics will compete with their reference products. State legislatures are considering, and some have already passed, laws that may affect the ability to follow-on biologic medicines to compete with existing biologic drugs.

Last year alone, at least 15 states considered bills governing follow-on biologics. The different laws provide some means for permitting interchangeable biosimilar substitution, but they vary in the effects and, some argue, the burdens associated with substitution. For example, this past fall California Governor Jerry Brown vetoed, as premature, a bill that would have permitted interchangeable substitution but would have required that a pharmacist provide the prescribing physician with notice. Meanwhile, Florida enacted a law that requires notification only to the person presenting the prescription, typically the patient.

A key question is whether such notification requirements and other kinds of restrictions have valid justifications, and, if they do, whether they are no broader than necessary to address legitimate concerns. Other regulatory efforts could also affect competition for biologics. Some parties are requesting that regulators change the existing paradigm for naming medicines that compete with an original reference drug.

In the case of traditional small molecule drugs, each brand name drug usually has at least two names, a proprietary, or branded, trade name and a non-proprietary name that's based on the drug's active ingredient. A small molecule generic drug has the same active ingredient as its reference branded drug. Which means that a generic drug typically has the same non-proprietary name as it's branded counterpart.

Biologic medicines in the US also have at least two names, a proprietary, branded trade name and a non-proprietary name that reflects certain scientific characteristics of the product. Some argue that biosimilars should have unique non-proprietary names that differ from the reference biologic's non-proprietary name. This naming process may have profound implications for how the marketplace will receive follow-on biologics and, therefore, will influence company decision making as businesses evaluate whether to invest in follow-on biologics development.

These regulatory choices will directly affect whether, and how, follow-on biologics enter the market, as well as how competition will develop once entry occurs. And they may also have crucial implications for patient safety. The ultimate goal, of course, is to develop policies that protect patient health and safety but to do so without unnecessarily chilling competition and deterring investment in follow-on biologics.

The FTC brings an important perspective to this dialogue. Our policy work in pharmaceutical markets dates back to the 1970s, as policymakers were grappling with how to regulate follow-on generic versions of traditional drugs. At first, many states responded by prohibiting pharmacists from substituting generic drugs for branded drugs. At that time, the FTC studied the competitive effects of state anti-substitution laws. A staff report concluded that the FDA's review process would result in the approval of safe and effective generic drugs and determined that if pharmacists were free to dispense generic drugs without unnecessary regulatory hurdles, then generic drugs would stimulate price competition that would benefit consumers.

Many states agreed with those conclusions and enacted the substitution laws that are essential to generic competition today. Now we see analogous questions raised about different state laws relating to biologics, biosimilars, and interchangeables. And let me emphasize the word

analogous. Biosimilars and interchangeables are certainly more complex than small molecule generics, but the basic principle of competition in the context of health care markets still applies.

We've convened today's workshop to explore both state laws and naming conventions, how they could affect competition for biologic drugs. We believe that, with necessary safeguards for patient health and safety, competition from follow-on biologics can benefit patients through lower prices and expanded access to important biologic treatments. So thank you for joining us for this timely and important dialogue, and I'm going to turn the floor over to Susan DeSanti. Thank you very much.

[APPLAUSE]

SUSAN DESANTI: Thank you very much, Chairwoman Ramirez. She is unable to stay because Congress has called to testify, which is one of the occupational hazards of being a chairwoman of the FTC. I'm Susan DeSanti. I'm formerly the director of the Office of Policy Planning and now an attorney with the FTC's office in San Francisco. Today we're here to discuss policy issues involving biologics and their potential substitutes.

As you heard from the chairwoman, biologics are obviously very valuable and also very expensive. And in light of their high costs, health care purchasers and consumers are interested in whether, and if so, when, FDA approved biosimilars or interchangeables could be automatically substituted for biologics, just as generic drugs can be automatically substituted for brand name drugs in certain circumstances. Which has saved US consumers and purchasers literally billions of dollars over the past 30 years.

Now, although, as the chairwoman mentioned, the market dynamics for biologics, biosimilars and interchangeables are likely to differ from the market dynamics for brand name and generic drugs, with lower discounts being offered than for generic drugs, it still appears that significant savings from competition could be achieved. And, indeed, Congress passed legislation that permits certain FDA approved biosimilars, those that the FDA determines to be interchangeable with a given biologic, to be substituted without the intervention of the physician, that is, automatically substituted.

So when we say automatically substituted, we mean the physician does not have to specifically give permission for the substitution. It's something that the pharmacist can implement at the pharmacy, and this is one of the primary ways in which generic drugs have led to so many savings. In fact, this type of automatic substitution happens thousands of times every day with FDA approved generic drugs. But that happens, in part, because there are state laws that permit that automatic substitution of FDA approved therapeutically equivalent generics, unless a physician writes the brand name on a prescription and specifies dispense as written.

So our first topic involves whether state substitution laws for biologics should operate in a similar manner. Now, the parameters have been set, to some extent, by federal law. Federal law describes two types of follow-on biologics. One is biosimilars. By statute, the FDA must determine, among other things, that biosimilars are highly similar to the original biologic.

Despite that similarity, however, biosimilars will require a separate prescription. Federal law does not provide that biosimilars can be automatically substituted for a biologic.

Second, there are interchangeable biologics, which federal law does specify can be automatically substituted for a biologic. And federal law has more stringent requirements for a biosimilar to be approved as interchangeable. Now as the chairwoman mentioned, currently in the US, the FDA has not yet approved either a biosimilar or an interchangeable and has so far provided draft guidelines only for biosimilars.

Nonetheless, some states have started developing laws that will apply to the substitution of interchangeables and, in some cases, biosimilars by reference biologics. This morning, we will discuss whether it makes sense to develop those laws now, and, if so, what, if anything, they should say to maximize competition and protect patient safety.

Now let me move to some introductions. As Chairwoman Ramirez said, we are very grateful to our accomplished speakers for their time and effort in preparing for and attending not only this workshop, but also the workshop in December. And I encourage all of you to read their very impressive bios, which we have distributed. Because we have a jam packed schedule, we decided to do all of the introductions for our panelists at the beginning of the morning and the beginning of the afternoon, so we reduce the time in transition from one speaker to the next. So we ask that as one speaker finishes, the next speaker should simply come up to the podium.

And as I give very brief introductions for our morning presenters and panelists, you can follow along in the agenda to see the topics they'll be addressing. Our first speaker is Aaron Kesselheim who will help us understand the statutory and scientific framework for the evaluation of follow-on biologics as compared to generic drugs. Aaron is an assistant professor of medicine at Harvard Medical School, a faculty member in the Department of Medicine at Brigham and Women's Hospital in Boston, and a primary care physician at that hospital.

Then Emily Shacter will speak about FDA practice related to biosimilars. Emily regulated therapeutic proteins at the FDA for 18 years, serving most recently as the chief of the Laboratory of Biochemistry and CDER's division of therapeutic proteins in the Office of Biotechnology Products. She now works as an independent consultant.

Next, Leigh Purvis will bring a consumer perspective to the issues around biosimilars. Lee is senior strategic policy adviser with AARP's is Public Policy Institute, where her work focuses on prescription drug pricing, biologic medicines, and prescription drug coverage under Medicare. Following Lee, we will hear about the current marketing of follow-on biologics from Ronny Gal.

Ronny, is a senior research analyst covering the specialty pharmaceutical industry at Sanford C Bernstein, which provides research for institutional clients. We will then have a 10 minute break, and I should emphasize that we will start precisely at the end of the 10 minute break so that we don't get behind on our schedule.

After the break, Jessica Mazer will provide us with an introduction to state laws related to biosimilar substitution. Jessica is the assistant vice president of state of affairs for the

Pharmaceutical Care Management Association, which represents prescription benefit managers, known as PPMs. Following Jessica, Geoffrey Eich will give the perspective of a reference biologics manufacturer on state substitution laws. Jeff is the executive director of R&D policy at Amgen.

Next, Steven Miller will speak from the perspective of a PPM that administers prescription drug benefits. Steve is senior vice president and chief medical officer for Express Scripts. Bruce Leicher will then provide the perspective of a biotech company, Momenta Pharmaceuticals, which seeks to develop interchangeable biosimilars, among other things. Bruce is senior vice president and general counsel at Momenta.

We will then have another 10 minute break. And following the break, we will have a one hour moderated panel discussion of state substitution laws. All of our morning speakers will join us on that panel, as well as some other representatives who I will now introduce, some of whom will also speak in the afternoon.

Bruce Lott is vice president of state government relations for Mylan, a leading generic and specialty pharmaceutical company. Mark McCamish is the global head of biopharmaceutical development for Sandoz International, a division of Novartis. Sumant Ramachandra is senior vice president and chief scientific officer of Hospira.

Marissa Schlaifer joined CVS Caremark as head of policy in April, 2013. She's a pharmacist with experience in both the managed care and community pharmacy segments, as well as leadership positions in other organizations. Krystalyn Weaver is a pharmacist and serves as director of policy and state relations at the National Alliance of State Pharmacy Associations.

After that panel, we will have one hour for lunch, and you are on your own for that. But there are a variety of sandwich shops and delis close to this building. And FTC staff will be happy to point you in the right direction get a quick lunch, and you should feel free to bring your lunch back here and eat in this room. Finally, after lunch, we're going to have an initial presentation by Elizabeth Jex, is the is prime mover and shaker behind this panel. And I'm going to introduce her now so she doesn't have to introduce herself.

She's going to give you a brief introduction to the naming topics that are the focus of the afternoon. Elizabeth has more than 20 years of experience investigating pharmaceutical, biotech, and medical device mergers, acquisitions, and intellectual property licensing arrangements. Her work on the FTC's 2009 follow-on biologic drug report won her one of the agency's top awards. And now, please welcome our first speaker, Aaron Kesselheim.

[APPLAUSE]

AARON KESSELHEIM: All right. Well, hi. Thanks to Elizabeth and Susan and Erin for organizing this and for inviting me. It's a pleasure to be here. And I guess I'm here today to start things off with a little bit of historical comparison between the issues that we're talking about today and a lot of the issues that have come up before in the context of small molecule drugs.

And so I think starting with a few quotes from stakeholders might be a good way to kick off the day. So here are some thoughts on the issue of interchangeability of pharmaceutical products. This is from a pharmacist, "From a technical standpoint, there's really no such thing as complete drug equivalence." A drug industry executive is quoted as saying, "Not only has the pharmaceutical industry been successful in maintaining the conviction with many physicians and buyers that not all drugs are alike, but it has even succeeded in persuading them that all products are different." And finally, from a congressman, who said, "I simply say to you that anyone suggesting that one drug firm is as good as another is a fool or naive or both."

The interesting thing is that I found all of these quotes in the context of the passage of the Hatch-Waxman Act in the early '80s, in the context of the interchangeability and substitutability of small molecule generic drugs. And looking back on that issue, those quotes now look somewhat quaint. The Hatch-Waxman Act, in 1984, had a number of different features to it. And I think that a lot of these features will come up again during the course of today's conversations.

The Hatch-Waxman Act created this abbreviated new drug application process that allowed a product to show that, if it had-- a manufacturer to show that if it's generic product had the same active ingredient, route of administration, and dosage form, that it could apply for approval from the FDA based on bio-equivalence data alone and did not have to go through the same clinical trials that the originator product went through, saving both time and money and also subjecting patients to trials that were unnecessary.

It provided the manufacturer with data exclusivity from five years from the date of approval of the original product, providing a guarantee period through which this competition through this abbreviated process was not allowed to begin, no matter what the status of the underlying patents. It provided this patent certification and litigation process that I think is not really going to be a lot of the basis of the discussion today. But I put it in there just for completeness' sake.

And, of course, a lot of people also don't necessarily remember that the Hatch-Waxman Act was a compromise between the generic and the brand name interests and also provided an additional market exclusivity period for brand name drugs in the form of patent term restoration. After the Hatch-Waxman Act was passed, the FDA established over the subsequent years rules for the establishment of this bio-equivalence process, that bioequivalent could be established on the basis of identifying maximum serum concentration of the drug, judging the area under the curve based on the serum concentration of the product, and establishing the general parameters that required a 90% confidence interval for the ratio of branded generic products. These were the basic principles that the FDA established, but it also provided some flexibility for the FDA's scientists to evaluate the particular circumstances around a generic small molecule drug and adapt their requirements to a particular circumstance.

So if a brand name drug caused nausea or vomiting for patients taking it in a fast state, then the FDA may not require necessarily fasted testing to go along with the fed testing. And so there were some flexibilities that were able to be established. And the outcome of this process of development, of these rules and regulations in the small molecule field was that, overall, over the subsequent decades, it became clear that small molecule bio-equivalents mirrored the clinical equivalents of the products.

And, indeed, there is no good evidence that generic small molecule drugs are less effective than their brand name versions as clinicians and patients have come to trust over the intervening decades. I've done a couple studies looking at this and looking at the specific literature, and here's a forest plot from one of these meta-analyses where we looked at cardiovascular small molecule drugs and, indeed, found that bio-equivalence does indeed translate to clinical equivalence in this field. And FDA reviews have shown that, even though their confidence intervals require this 10% boundary, that most small molecule drugs come within a much tighter interval than even the regulations require.

So the outcomes of the Hatch-Waxman Act were fairly astounding over the next few decades. The percentage of generic drugs prescribed, which was as low as 19% at the time leading up to the passage of the bill, rose to about 50% of all prescriptions by the year 2000. And more recently, small molecule drugs make up about 84% percent of all prescriptions-- generic small molecule drugs make about 84% of all prescriptions for small molecule drugs. And a recent report by the GAO suggested that this system has saved the health care system \$1 trillion dollars in unnecessary spending over the last 10 years.

And then this chart on the bottom shows approval of new molecular entities by the FDA over the last five decades. The passage of the Hatch-Waxman Act comes about halfway through the chart there. And what you can see is that the number of originator products approved by the FDA in the years following doesn't diminish and, indeed, rises up until there's this peak in the mid '90s, and then it comes back down to the historical mean. But overall, the amount of innovative new products coming through the FDA remains fairly consistent.

Nonetheless, one of the most impressive things to me is how successful the Hatch-Waxman Act has been despite the multiple barriers that exist in the marketplace to generic drug use. Surveys of physicians and patients even today show that there is substantial skepticism on the part of physicians and patients when they hear the word "generic" and hear the term "generic," despite the fact that generic small molecule drugs are so prevalent.

There is substantial marketing on behalf of brand name manufacturers, some of which is explicitly anti-generic. And anecdotal and lay media reports providing skepticism-- again, in the face of no evidence to the contrary-- providing skepticism about the safety of generic products. And the generic products industry has flourished despite the fact that estimates suggest that brand name manufacturers spend about \$60 million a year marketing their products, and the same outlay is not spent by the generic small molecule industry.

There are studies that show that physicians don't know about the cost of drugs to their patients and tend not to talk about them with their patients. So that conversation isn't necessarily happening at the level of the physician. And there are also studies looking at physicians' prescribing practices suggesting that 80% of them continue to use the brand name product when they're referring to multi-sourced drugs for a generic product.

So how is it that the Hatch-Waxman Act has been able to have such an incredible impact on the generic small molecule marketplace? And the answer is because of the state drug product selection laws that allow, in some cases, automatic interchange, in other cases, permissive

interchange of A rated generic products. So if the FDA approves a generic drug as pharmaceutically equivalent to the brand name product, the generic gets its therapeutic equivalence code and the automatic substitution is allowed to happen at the level of the pharmacy.

Now, there is variability among the various states in their code. Some states have a mandatory system of substitutability, others have permissive substitution. Some require patient consent at the level of the pharmacy as opposed to calling the physician and requiring the physician to change the prescription. A lot of this patient consent can happen at the level of the discussion between the pharmacist and the patient itself. So there is some variability in these drug product selection laws.

And there's limited evidence about the effects of these laws as well. So we did a study looking recently at this question and found that variability in the state drug product selection laws does lead to substantial differences in small molecule generic use rate among patients within those different environments. And we found a 25% lower substitution rate among Medicaid patients in states that had patient consent requirements-- that required before a pharmacist could substitute a small molecule product.

And we estimated that if you only looked at three top selling small molecule products, Lipitor, Plavix, and Zyprexa that this difference could lead to over \$100 million in excess spending in Medicaid alone, which is only about 10% of the total US drug spending, in the first year after generic entry. In the same study, we found that the costs of prescription drugs are much lower in the states without patient consent.

And other studies have shown that some of these state laws initially required substantial record keeping in addition to consent and that this extra record keeping requirement on the part of states also led to lower substitution rates by pharmacists that didn't have the capacity to do that. Evidence in other fields of small molecule drugs where non-A rated approved generic drugs have been approved by the FDA suggest that there's less competition, lower savings, and less substitution of these non-A rated generic drugs that are then-- where there's then competition between the generic and the brand name product instead of just substitution.

So now we get to the topic of the conversation today, which is the Biologics Act. And, again, the Biologics Act in many ways mirror the principles provided in the Hatch-Waxman Act, and there provide two levels of biosimilarity, highly similar and interchangeable, which I know, again, over the course of the day, we'll talk a lot more about. And the other aspects of the Biologics Act also did mirror some aspects of the Hatch-Waxman Act, including the patent dispute resolution process. And it provided a 12 year period of guaranteed exclusivity before any follow-on product could be authorized.

So I want to end in my last couple minutes with what I think are three lessons from this story about the comparability of the small molecule and biologics market. First, that FDA biologic drugs are potentially scientifically viable and can be used interchangeably. In fact, there's a great deal of experience so far with some relatively limited biologic drugs that have been approved through the ANDA, the Hatch-Waxman process.

Here's one example. Generic Calcitonin nasal spray, which is a polypeptide hormone that's used in osteoporosis made up of 32 amino acids and a disulfide bond. When the FDA was considering this product, the questions that they asked themselves, do we need to require in vivo immunogenicity testing? Do there need to be clinical trials showing a similar clinical effect between the brand name and generic product of this? And the FDA ultimately reviewed the science and determined that these sorts of testing was not necessary and allowed chemically synthesized generic versions to be approved, on the basis of the fact that the impurities were, in this case, easy to characterize, monitor, and control and that the primary structure was a major driver of the structural ordering of this complex molecule.

Another example that I know we're going to hear a lot more about today is generic Enoxaparin, a mixture of oligosaccharides used as an anticoagulant. The FDA approved the generic in 2010, again, not on the basis of formal clinical trials, but on the basis of five principles that, again-- after an investigation into the science of this to determine if these things could provide a product that is safe and effective in the marketplace. And so, if these five different requirements were met, then no additional clinical safety or efficacy data would be necessary and consumers could feel confident.

So, indeed, there's also been substantial European experience so far in this field. Since the first European follow-on biologic was approved in 2006, there is now experience with about a dozen follow-on products made by four manufacturers in Europe in the epo and human growth hormone spaces. And so I think the general principle here-- now, again, these are the successes. There also warning cases out there where immunogenicity has emerged, but I think that the ultimate lesson here is to follow the science, that interchangeable biologics are possible in some cases, not possible right now in other cases. And as the science evolves, these principles will be able to change, and the regulatory sphere and state laws should be able to adapt to the fact that science will continue to evolve in this space, and the FDA has access to and will continue to gain expertise necessary to make these decisions.

Second of all, the science, although important, is not enough. The name is actually critical. And that's state drug product substitution laws. And the similar namings of the small molecule and brand name products were key to the implementation of the Hatch-Waxman Act. Non-interchangeable generic drugs have limited market penetration, higher costs, and reduced savings.

And that's because, even today, it remains true that the public is skeptical about things labeled generic. And generic biologic drugs will have to compete by providing a substantial investment into marketing against the brand name products if there isn't a sort of interchangeability that's allowed. And so blanket state anti-substitution carve outs are highly problematic for those products that the FDA, using currently available scientific tools, has judged to be interchangeable.

And then the final lesson is that creating a viable generic drug market-- I think is the goal for part of the discussion today is talking about creating a viable product market in biologic drugs-- that did not reduce brand name innovation, that the five year data exclusivity period was effective for maintaining strong innovation in the small molecule field, and that the 12 year period in the

biologics space may actually be much longer than is necessary, because I just wanted to end my comments with the thought that the end of the market exclusivity period is what drives innovator companies to develop new, genuinely improved products that will contribute to the next generation of therapies and medical progress. Which is, I think, what everyone today is here to talk about. Thank you.

[APPLAUSE]

EMILY SHACTER: Good morning, everybody. I am Emily Shacter. I was at the FDA for 18 years and regulated protein products almost exclusively during that time.

About 10 years ago, I took an interest in what, at the time, was called follow-on biologics and started immersing myself in that subject, initially, from a scientific perspective, since I ran a research lab for my entire career until the day that I left the FDA, but also, eventually, taking an interest in the policy issues that came up over the years, which allowed me to contribute in one way or another to the FDA draft guidances that came out a few years ago. I have a couple of FDA colleagues in the room, and they can either support or correct anything that I have to say today, but I will focus on the science of the issue.

So what I'll talk about is FDA's approach to the review and regulation of biosimilars. I have to say, in our training in CDER, the Center for Drugs, which is where I left-- I started out in the Center for Biologics-- we had these two screen situations, which are a nightmare for somebody who likes to actually connect with the audience. And you kind of feel like this bobbing doll that you're looking back and forth at the screens, but also now having a third screen, I can't even access you over there so I apologize to the people in the far side of the room.

So I'll also talk about the role of analytics in the development of biosimilars-- yeah, see. That's the problem. You can't like-- good. Thank you. All right. And then I'll talk about, how do we make a scientific determination about when a difference matters and when it doesn't? To get back to the definition, then, of what is a biosimilar as defined in the statute from the BPCI Act. And I've abbreviated the definition for the purposes of conversation.

What I want to point out is that a biosimilar protein product has to be highly similar to the US license reference product notwithstanding minor differences in clinically inactive components. And there has to be a demonstration that there are no clinically meaningful differences. So two places in the statute the term "difference" is used, and I'm going to talk about that in just a moment because it's very important.

But first let's talk about how a biosimilar is made, and there are many people in the room here who have actually done this. I personally have not, but the folks here in the audience can speak to this actual process. So first, you choose the US license reference product to which you want to make a biosimilar, you characterize many lots of that US license reference product to determine, what is this protein? What does it look like? And what are the critical attributes of this product that are responsible for its clinical activity?

Then, you try to make your own product. You reverse engineer your biosimilar product to try to match what you've understood about the US license reference product. And if you find differences that appear to be significant, then you're going to try to manipulate either the cells that generate that product or the process that's used to make the protein product, in order to try to match as closely as possible the reference product that's on the market.

Any differences that you see that raise uncertainties about what the predicted clinical performance of that product will be addressed through a variety of different kinds of studies, including functional studies, the bioactivity of the protein, non-clinical, and potentially clinical studies. The fact is that thanks to the power of today's analytical techniques, small differences between a biosimilar and a US license reference product are expected, unavoidable, and will be detected.

The challenge is how to rigorously justify-- this is the responsibility of the sponsor making the product-- how to rigorously justify any observed differences in order to ensure that there are no clinically meaningful differences between the products. And that doesn't mean words. It means that actually that product will perform clinically the same way as the US license reference product in all important aspects. According to the FDA scientific considerations guidance, it came out that in 2012 there are three different kinds of studies that go into the assessment of similarity.

One is the analytical studies, which is area in which I have my greatest expertise. One is animal studies or non-clinical studies to evaluate the activity of the product or the toxicity of the product in a small animal model system or also non-human primates. And then the clinical studies, which will include pharmacokinetics, PK, pharmacodynamics, PD, and immunogenicity, in order to ensure that there actually are no clinically meaningful differences.

The agency has the discretion to determine that any element of these three components can be waived if there actually are limited uncertainties about how the product will perform clinically. And this is very important because the FDA now has discretion to determine, well, what is a highly similar product? In my opinion, and given my experience working on biosimilars for many years at the agency, the FDA is not going to waive any element of that analysis if there is any residual uncertainty that the product will have basically identical clinical performance compared to the US license reference product.

They're not going to do that. How are they going to make these determinations? Well, first of all, these are very experienced reviewers that are going to be analyzing all of these submissions. Think about it. They have seen every protein product that has come through the agency. And so they have deep knowledge of protein products and what to expect from them and what's important, what isn't important.

There will be numerous internal meetings and working groups to determine, what are the important aspects of the protein product? There will be multiple levels of supervision to make sure that the messages are clear and consistent across products and to different sponsors. And importantly, there's a lot of cross-disciplinary team work so, as a group, the CMC reviewers, the non-clinical clinical reviewers, and the clinical reviewers, and our legal folks, of which we have

some here in the room, can make a determination that a product should be approved as a biosimilar.

In my opinion, also, the FDA is only going to approve a biosimilar that can reliably be expected to perform clinically similarly to the US license reference product. They have no motivation to do otherwise. So, although biosimilars don't meet an unmet medical need except for access and cost-- so that is an important medical need, but many of these clinical reviewers, for example, would rather be working on, let's say a breakthrough product, for example. Because they want to actually deal with issues that have not been met clinically for patients.

So they have very little motivation to approve a biosimilar if it's not highly similar to the reference product. The agency is conservative by nature and very risk averse. The agency is particularly risk averse to having one of the first biosimilars out of the gate actually end up having clinical problems and clinical differences. Because this would really sink a program in which there has been tremendous effort, conscientious effort put.

So there's a lot of risk aversion to approving a non-highly similar biosimilar protein product, and so all scientific expertise will be brought to bear. And any residual uncertainties that the biosimilar will behave similarly to the reference product will have to be addressed by various kinds of studies. In my opinion-- and I'm outside of the agency, but that's a good thing. I can say whatever I want. I think that this really insures virtual interchangeability. Now, maybe not in all cases, but if a product is approved as a biosimilar by the FDA, the FDA is pretty darn certain that it's going to behave clinically highly similarly to the reference product. They're not going to let it out if it doesn't.

I'm not an expert in the laws and all of that, but in terms of how a product is going to perform clinically, I do have a lot of experience, especially in protein products. So they're going to be virtually interchangeable. Now I'm going to shift to analytics because this is my greatest area of expertise and bring forth the fact that I remember 10 years ago when we were talking about follow-on biologics. And there were some legitimate arguments as to whether the analytics were sufficient in order to be able to highly characterize a protein product well enough to be able to say that it's highly similar.

That was 10 years ago. Analytics have progressed so much in the past 10 years that, in my opinion again, it's not really true. It's the power of analytics that have even made biosimilars a reality today. Consequently, and for many reasons that I'll explain, the foundation of the similarity assessment is the analytical studies, because this is the part that we can best characterize.

So why is this? Well, analytical studies evaluate a protein product down to the atomic level. Every aspect of a protein product will be evaluated. They are highly sensitive and highly discriminating to determining whether there's a difference between the protein product and the reference product. This is very different from animal studies, which were much more crude.

They serve an important purpose in certain cases, but you need to use a lot of animals in order to make a discriminating determination of similarity and difference. And that's not the way most

non-clinical studies are done for biosimilars. Six animals in a group. What are you going to do? The reviewers hardly know what to do when a difference is seen. And then clinical studies are even less discriminating than analytical studies. So the clinical studies, especially safety and efficacy studies, have to be quite large in order to be able to detect the difference between two products. And everybody in the room knows this.

And so it's the analytical studies that have the most discriminating power. For this reason, if there is a significant difference in the molecular attributes of two protein products, they actually can't be overcome by clinical studies. And this is the main reason why the FDA came up with this-- and I was in the agency at the time-- this pyramid paradigm.

Where, if you look at the right hand side, this is really the desired program for development of a biosimilar protein product, where you have extensive analytical studies, relatively minimal non-clinical studies. Then you have your clinical pharmacology studies and pharmacodynamics if you have a relevant model. Those actually will be pivotal studies, and there's going to be no getting around those for the foreseeable future.

And then using additional clinical studies to reduce any residual uncertainty and, if necessary, to also look at immunogenicity. So this is the paradigm and this is the foundation that's being followed, analytical studies. How do you get a reduced non-clinical and clinical requirement for developing your protein product as a biosimilar? You have to demonstrate to the FDA and convince them that your product is highly similar to the US license reference product.

That ain't easy. But it can be done. And when I say, it's not easy, I say that because the FDA is setting a high bar. And I think my FDA colleagues in the room can attest to that. So speaking of the analytics, so what is a protein, for the lawyers in the room?

It starts with the amino acid sequence, which comes from the gene that's used to generate the protein product in the host cell that's doing it. It takes on what's called secondary structure, which is the form that these amino acids naturally take next to each other. So alpha helix, beta sheet, and then it folds into the active way that is actually responsible for the clinical activity of the product. It's also what the body sees.

So it's this folded protein that's an active. If you boil it and you lose that folded structure, you lose activity. You'll have the same amino acid sequence, but you won't have the same clinical activity. And then also if you have a multi-subunit product, for example, like a monoclonal antibody, then it's the coming together of those different sub-units that's also extremely important.

So I call these two here the higher order structure-- actually three of these-- higher order structure of the protein product. Without that highly similar higher order structure of the protein product, you will not have the same clinical activity. And you may run into immunogenicity issues with the product. Protein products are extremely large. There are many amino acids, almost unaccountable compared to a small molecule generic drug. And there are many ways where-- I'm sorry. I can't point over there.

There are many ways in which the protein product can be changed. I won't go through this list. You have the slides, but many different aspects of a protein product. So actually a protein product is a mixture of heterogeneous molecules that have a lot of similarity to each other, but you don't have a population of identical molecules. So even that is an exercise in analytical discrimination. What is my population of protein products?

The good news is that, thanks to today's analytics, protein product can be deeply analyzing and characterized. So the complexity that you find in our protein products can be addressed with a large array of powerful analytical techniques. If this were not true, we would not be having biosimilars today. We wouldn't be talking about it. There would be too much risk.

And, again, I won't go into this list. You have it as a reference, but basically this is to sort of summarize some of the many techniques that we have available to analyze every single aspect of a protein product. And I would say that, today, the only two elements that we can't fully predict are immunogenicity-- and we still have some issues in determining the folding of protein products given that you have a mixture.

That doesn't mean that that inability isn't overcome in many ways, but we don't have perfect analytics to comprehensively evaluate every aspect of every molecule in a protein product. But one of the techniques that I'd like to show is, for example, these studies that came out of my colleagues in England looking at the higher order structure of a crystalline protein.

And what they did is they wanted to determine whether this technique for higher order structure-- this is a circular dichromosme-- can actually tell if you have a single mutation in a protein product. And so they introduced a mutation into one amino acid and looked at the wild type and then two different mutations, one of which had a change, an influence, on higher order structure, one of which didn't.

And if you do the technique right-- as for any technique, if you do it right-- you can tell if you have a difference or if you have a similar protein product. I'm getting flashed my five minutes. Monoclonal antibodies are among the most highly studied products that we have on the market. And even though they're large and complex, we know an awful lot about monoclonal antibodies and what the various different amino acids in this large molecule do to contribute to its clinical activity.

So what do you do if you do find differences between your biosimilar protein product? You have to determine if those differences might be impacting clinical activity, and you'll do this through multiple analyses of biological activity and also looking for potential impact on PK. So it's not just the activity, but you also have to make sure that the biodistribution of the molecule is the same.

How do you do this? State of the art analytical techniques. You have to be able to detect and characterize the molecule so that you know if you don't find a difference, it's because you applied the correct analytics. And in fact, there is no difference and not just that you used poor techniques. Sponsors using blunt analytical techniques need not apply. Now, while I was at the

agency I saw some, let me say, sub-par submissions regarding characterization of protein products. And they need to go home and do a better job.

And so in the end of the day, you're going to put together all of your powerful analytics to be able to determine whether you have a similar or different protein product. So the similarity assessment will be comprehensive. There's going to be a deep analysis and comparison of the biosimilar to many lots of the US license reference product. Different state of the art analytical methods will be applied. There will be stress testing to make sure that there isn't some buried difference in the molecule that you can't detect by just looking at the molecule on the surface. And the latest paradigms for the sensitive and-- for sensitive clinical pharmacology studies will also be applied. And one day we will actually see the clin-pharm guidance document coming out.

So I would like to-- just a couple more points. I think that the old stories about how we had unexpected and adverse events from protein product. In other words, adverse events that did not derive from the expected pharmacological activity of the molecule, because that's where you have most of your adverse events with proteins. It's the pharmacological activity of the molecule.

So there's a famous case of Eprex, which caused a very severe disease, actually, in patients who received a product that underwent a manufacturing change. Unexpected immunogenicity of the product had knocked out a physiological system. I don't think those events are going to happen. Let me say this, I think the likelihood of those events happening is greatly reduced today compared to what it was 5, 10 years ago. And that's because we have better analytics and we have more extended use of the analytics.

So on the comment of immunogenicity because this is important. And it's used as a reason for why a biosimilar protein product actually might be unsafe, because you don't have the same extent of clinical studies. Well, this could be true. But what does immunogenicity come from? It comes the amino acid sequence, the folded structure. It's essentially what the body sees of this molecule after it gets injected into the system. And the immune system is actually one of the best discriminators of similarity and difference.

The immune system has such a great capacity to tell if proteins are similar and different. So this is extremely important, and the consequences of immunogenicity can be many. You could lose efficacy, as has been the case in some cases where you lose the activity of the protein product of interest. You can knock out a physiological system as happened with thrombopoietin and erythropoietin. You can have hypersensitivity reactions, et cetera.

Most licensed protein products do have some level of immunogenicity. Most of the immunogenicity is inconsequential. I think, in many cases, it actually knocks out the ability for a patient to be able to use drug, so you want to have some back up drugs that are similar but different in order to be able to compensate for the loss of that activity. I'm getting my flag for one minute left.

So I would like to close by saying that FDA approved biosimilars, in my opinion, will be among the most deeply analyzed and predictable protein products to hit the market. Maybe one exception is Enoxaparin and some of the folks who were responsible for developing that drug.

That was certainly deeply analyzed as well, but it's really a paradigm setter for the discussions that we're having.

So will they be determined interchangeable by the FDA? I don't know. I'm on the outside now. So this is to be determined, but I can assure you that all scientific rigor will be brought to bear. So I want to just thank my former colleagues from the Office of Biotech Products and the Office of Generic Drugs, and actually a couple of my legal friends here in the room, Janice Weiner, with whom I worked very closely at the agency, for helping to inform my opinions about biosimilars. Thank you very much.

[APPLAUSE]

LEIGH PURVIS: Hi, my name is Leigh Purvis I've-- closer? OK. My name is Leigh Purvis, and I've been asked to come here to provide the consumer perspective on the issues being discussed today. I'd like to start off with explaining why biologics and biosimilars matter to our 40 million members.

First and foremost, I think it's very clear to us and probably clear to everyone in this room that biologics represent the future of the drug industry. There are a growing number of products on the market, and there are hundreds more in development. We've also seen projections that they're eventually going to represent more than 50% of spending in the next few years.

We also are aware that there are a large number of popular biologic products that are either off-patent or due to go off-patent shortly and, thus far, we haven't seen any sort of impact or noticeable change from that. Something else that's caught our attention is that, for the products that are on the market already, there are a rapidly increasing number of indications, sometimes dozens for a single drug. So, basically, more of them are coming to market, and more people are using the ones that are already here.

I think it's safe to say that one of the primary reasons that AARP is interested in biologics is their remarkably high costs. The average annual cost of a brand name biologic is estimated to be roughly \$35,000 right now. However, annual costs can range anywhere from \$25,000 to \$200,000 or more, with many drugs coming on with prices at the higher end. For example, 12 out of the 13 new cancer drugs approved last year were priced over \$100,000 annually. And some drugs are coming to market with prices closer to \$400,000.

Something you've probably heard us say repeatedly in public when we're speaking on prescription drug issues is that older Americans use more prescription drugs than any other segment of the population. Over two thirds are taking three or more drugs and three quarters are taking two or more drugs. So they're a population that are using a lot of these products.

Also, biologics are used to treat conditions that are more commonly found in older adults, many of which are chronic conditions. So when we talk about our members using biologics, we're talking about people who are probably going to be taking them for the rest of their lives. Now, to put some of the numbers I'm going to be presenting next in context, I wanted to start off by dispelling some myths that seem to be out there about Medicare beneficiaries.

Number one, they are not wealthy. Their median income is just over \$20,000, and more than 25% have less than \$10,000 in savings. So we are not talking about people with substantial assets. Second, they are not in good health. More than two thirds are currently being treated for concurrent chronic illnesses.

So the Medicare program, which is a topic of constant discussion for us-- Medicare Part B, which generally covers services associated with doctor's visits, is spending a lot of money on biologics. Under Part B, beneficiaries are responsible for 20% of their prescription drug costs, and there is no out-of-pocket cap. So anyone taking a biologic facing 20% of cost is going to be facing that same scenario playing out year after year.

I've heard people respond to our concerns by saying, yes. Well, the vast majority of Medicare beneficiaries have supplemental coverage, and that is the case. However, the 12% who don't are in serious trouble, and for those that do have supplemental coverage, it's not like the costs associated with these products just disappear into the ether. They will come back to beneficiaries in the form of higher premiums or cost sharing, which could ultimately make that type of coverage unaffordable.

Or alternatively, if they have supplemental coverage from a taxpayer funded program like Medicaid, it increases government spending. And, of course, we also have concerns about the Medicare program in terms of its longevity. And the 80% share of the cost associated with biologics that's shouldered by Medicare is not sustainable.

Another part of Medicare that we spend a lot of time on is Medicare Part D, which covers outpatient prescription drugs or those that you tend to pick up at the pharmacy. Under Part D, a lot of plans are increasingly using co-insurance, or where the beneficiaries are responsible for a percentage of the cost as opposed to a flat co-payment. That co-insurance tends to range from 25% 33%, which can be thousands of dollars for a drug that's extremely expensive and is particularly expensive for someone who's on a fixed income.

And, fortunately, unlike Part B, under Part D there is an out-of-pocket cap, a catastrophic cap of around \$4,500. Unfortunately, in order to reach that, you're spending roughly the equivalent of a quarter of a Medicare beneficiary's median income on just Part D cost sharing, which obviously is problematic. It's also worth noting that, even after you reach catastrophic, you're still responsible for some level of cost sharing, for example, Humira, a common biologic, the cost sharing associated with catastrophic is still over \$100 a month.

We also have noticed that there is no real incentive for Part D plans to control spending on biologics because a beneficiary who is prescribed one tends to blow through the benefit pretty quickly, and after catastrophic, the Medicare program is on the hook for 80% of cost sharing, again, much like Part B.

We also keep track of private insurance. We have a lot of beneficiaries who have employer sponsored coverage. And typically where Part D goes, employer sponsored coverage tends to follow. So we're seeing an increase in co-insurance. We're also seeing an increasing number of

plans that have created a fourth or even higher tier with an average co-payment around \$80 and the average co-insurance around 32%.

This population is different. They're typically not on a fixed income, but paying for a third of a drug that costs thousands of dollars is not going to be easy regardless of your income. And it can be difficult for even those with good insurance. Something else we've noticed is reports that the relatively low cost sharing associated with biologics is threatening to increase cost sharing for drugs that are non-specialty. So, basically, the small-- relatively to the cost of the drug-- the amount the beneficiary is paying is actually pretty low, and if it's going to maintain that same level, it's going to increase cost sharing across the board.

We've also been keeping an eye on the plans that are going to be offered in the exchanges. The beneficiaries under those plans will benefit from new out-of-pocket maximums. However, a lot of the exchange plans are going to be relying on co-insurance for tier three and tier four, which can result in extremely high cost sharing. For example, you can see here the average cost sharing is around 40%, but it can reach as high as 50% or 60%.

That level of cost sharing could put drugs out of reach for a vast majority of Americans. However, saying all of this, while cost sharing is a problem, the underlying problem is the cost of the products. Even if the cost sharing were held lower, the costs associated with these products would eventually come back to consumers in the form of increased premiums.

Something else that is usually pointed out to us when we raise concerns about the price of drugs is patient assistance programs. We do find them helpful. However, they can be less than generous. They typically do not help insured patients, and they tend to have very low income thresholds. Some also require beneficiaries to spend a certain amount of their income before they can participate. Each company has their own qualifications, their own forms, their own processes and rules for refilling. They can even have a different program for each-- a single manufacturer can have different programs for each drug. The net result is the kind of complicated system that can make it difficult to access certain drugs.

So, as evidenced by this meeting, the passage of BPCIA obviously did not signal the end of the issues surrounding biologics and biosimilars. And AARP still has a number of lingering concerns. Probably first and foremost, the one we've been most vocal about, is exclusivity. Our long-standing position is that the 12 years provided by BPCIA is too long.

We've also been surprised by a lot of debate over the definition of what type of exclusivity was provided on BPCIA. Is the 12 years data exclusivity or is it market exclusivity? Something else that's been brought to our attention repeatedly is the risk of evergreening. I understand there have been people saying, yes. That's never going to happen, but we've also been hearing a lot of concerns that it will. Another concern is the possibility of reverse payments. Unlike Hatch-Waxman, BPCIA does not require companies to report settlements to the FTC.

As far as what we're mostly discussing today, briefly-- I know it's going to be discussed in greater detail. So I will just provide AARP's perspective on it generally. And that is that we think

that the state legislation that we've been seeing is designed to make interchangeable biosimilar substitution so onerous that prescribers and pharmacists don't bother trying.

We also don't understand why it's necessary, given that the FDA has yet to approve a biosimilar. Our feeling is that if we can trust the FDA to regulate and approve biologics, we can trust them to approve and regulate biosimilars. And we have yet to hear a valid reason why substitution should not be the same as it is for traditional chemical-based drugs. If this legislation were to be enacted-- and in some cases, it has been-- our feeling is that it's going to reduce substitution and subsequent competition that is needed to reduce the costs associated with these products, and it's going to increase health care costs across the board.

The AARP perspective on naming is rather similar. We're not quite sure what the rationale behind it. We think mostly it's going to leave to prescriber and patient confusion and possibly impact patient safety.

We also think that it kind of is intended to create the false impression that biosimilars have a different clinical effect than the original biologic drug, and we also have some serious concerns about the fact that having different names that separate the existing safety information from the biosimilar. And, again, we believe that different INNs would reduce substitution and subsequent competition, which, again, increasing health care costs.

So how do we see things in the future? I think our biggest concern is whether the stated purpose of the BPCIA Act is going to be fulfilled. Supposedly there's going to be price competition, but there seems to be a lot of activity on the market that might thwart that. Another concern is whether the pathway will actually be used.

We have heard FDA saying that some people have started the approval process. However, we've also heard a lot of companies saying there are so many problems with it, they don't intend to use it at least for the foreseeable future. But I think the biggest concern is that we want to make sure that competition develops. And right now, we're not quite sure that it will. There seem to be a lot of roadblocks that are being thrown up. It makes it less likely that companies that could potentially provide biosimilars will actually enter the market.

Another concern that's come for attention is that this might just be to tip of the iceberg. There might be other opportunities for additional delays in the market. For example, a biologic manufacturer might decide to kill their old product and launch next generation product just as soon as the biosimilar competition approaches. Another option would be constantly tweaking the reference product which would preclude substitution indefinitely.

They could also compete on price, since they already have the manufacturing facility set up, which kind of reduces the incentive for a biosimilar company to enter the market. And, finally, something we may already be seeing. They could raise fears of reduced efficacy or increased risk of side effects from biosimilars.

So what if this never happens? What if the market never develops? Well, for the first, I think the one word that we constantly hear related to prescription drug prices, particularly biologics, is that they're not sustainable for patients or payers. Something has to change.

I think if nothing happens, more patients, and many patients, may not be able to afford biologics if competition does not provide some level of price relief. And I think one final thought that we need to keep in mind for the rest of the day is that the best medical advances in the world are meaningless if no one can afford to use them. Thank you.

[APPLAUSE]

RONNY GAL: Good morning. I'm Ronny Gal. I'm an analyst with Sanford Bernstein. My day job is to predict the success, commercial success, of drugs and drug companies. And I come from a perspective of Wall Street, which is we don't really care if certain drugs do well, biosimilars do well, innovative drugs do well. Our job is simply to predict it. And I've done most of my research for the last three or four years looking at biosimilars first from a viability perspective and not from a commercial perspective, based primarily on the history of small drug molecules and what we know right now about adoption in Europe and the technology.

I'm going to make three points here. The first one is around the commercial rationale from a corporate perspective about developing biosimilars. The second one is what we can learn from adoption in Europe. And the third one-- some observation about the current US drug system and the holes are in a bit of that, essentially, producing opportunities to delay biosimilars.

So first, when I went to school and studied biochemistry, the process of making monoclonal antibodies and other drugs was very much of an art. That has changed over the last 30 years. A successive process of standing on the shoulders of giants and engineering improvement have turned the process from an art into a science. The skills required to make biological drugs have advanced to the point where you can actually outsource most of the manufacturing and even development of the drug and get a reasonably quality answer.

The other thing that happening parallel was a great reduction in the costs of making biological drugs. As yields improved and processes got to be more scientifically sound, the costs of making drugs greatly decreased. What did not decrease and actually increased with successive generations of drug introduction was the price. So price points of biological drugs, as we heard from previous speakers, \$25,000 to \$200,000.

Gross margins are actually running now in the high 90s. So the cost of making biological drugs coming out of the facility net of whatever royalties you have to pay universities is right now about 2% to 4% on average of the price of actually being obtained realistically, in the marketplace and realized prices. If you are basically a drug company, and you look at this and you go, hmm. 96% gross margins. Patents are about to expire on the first generation of biological drugs. Obviously the law of economics dictates on very large revenue drugs that you will seek to develop the follow-on product.

Skills are available to be hired. Money is available to be gained. And therefore, companies go out and try to develop this. Two side effects of this process. Obviously, if you're the guy who owned the original molecule, guess what? You will try to innovate a way and improve the molecule to a better drug. And one example I will give is Roche who have done a wonderful job of improving their Herceptin and reduction franchises with the new generation of drugs.

And second, innovation in manufacturing to produce at low cost and higher quality. Previous speakers spoke about the quality of analytics. I would argue the quality of analytics has to do to a large extent with the need to better characterize your drugs for the process of making biosimilars. This actually was a push for the analytical science that you had to get to that level of accuracy.

Second, adoption in Europe. The short answer-- the one background word I would say here is that the EMA has been a lot more aggressive than FDA in terms of developing biosimilars. As a matter of fact, the first slide they always put up when EMA people speak on the issue of biosimilars is the cost and the imperative to reduce costs. FDA has been a lot more shy about actually using the directive to reduce costs as a rationale. EMA has been very open that their objective is to help in reducing health care costs in the countries which they serve.

Adoption of biosimilars in Europe has not been even. That is the point I'm trying to make here. This is the May, 2012, prospective. Even with the availability of biosimilars, it's critically dependent on the set up in every country in how they pay for drugs and who decides how drugs are reimbursed and the influence national payers have on the decisions by physician what to prescribe. OK.

So, , essentially, the availability of product is necessary but insufficient to drive adoption. Biosimilars can easily fail. And what we've done is we spoke with a bunch of payers, individual countries, and a bunch of pharmacists. To give you two examples, I spoke with a doctor in the UK who is in charge of the National Health Care Trust and he basically says, look. There's NICE guidelines. If NICE tells me I can use this product and it's cheaper, guess what? I'm using it. Britain also has INN naming.

I spoke with a pharmacist in a hospital in Italy about the use of anti-TNF drugs, and to asked her, what is done when you're running out of budget in mid-year? Her answer is, well, my job is to find budget. The doctors get to prescribe what they want. And my job is to find the budget to allow them to prescribe what they wanted. It was not, I need to manage the budget. So differences in countries.

And, by the way, I'm not picking on Italy. This is all clearly changing because of the economic crisis in Europe. But clearly the approaches by different payers and different health care systems matter dramatically for adoption of those products.

Third, about the emerging dynamics in the United States. So one thing I would say, clearly the drug companies have picked up the mantle of developing those biosimilars. If I look at the league table of companies, almost each and every one of them has some sort of a biosimilar initiative.

Now, this is the May, 2012, picture. We keep on updating it, and we're always running three months behind just because there are at least 10 highly credible biological manufacturers who are involved in making biosimilars. There clearly is an interest in coming to this market. And when I first saw that, I said, aha. We're going to have those products coming out. There will be multiple of them. Therefore, the prices will come down, and, therefore, this would be a great benefit to the US system and frankly great reduction in cost to the consumers and it was all great.

As the last couple of years progressed, my opinions have become a lot more sour on that thought. I am now far less convinced that biosimilars will have the impact that one would hope they would have as a cost reduction for the US consumer. And I'm going to mention essentially some barriers, and this is far from an ultimate catalog. But slowly there's a bunch of things you can do before a drug comes to market, in terms of changing your reference product, introducing new IP that most of the world would not be given, but in the US would.

There are some bugs in the US patent system that allow for patents to progress for a very long time before they're actually issued. This is now changed with some new changes in IP law. But it will clearly influence the first generation of molecules.

And there are, essentially, multiple other tools I haven't even thought about about challenging the law that just passed. We know that the Hatch-Waxman law went through about 20 years of court challenges and fixes before it got to where it is today. The first generation of biosimilar law will almost certainly have to go through the same round of adoptions.

But a more interesting question is, what will actually happen when those drugs come to market? And there is a variety of barriers for adoption that already exist today, and I'm going to just give you two examples. I'm just putting this long list as a catalog of problems we've already identified. And I'm just going to mention two of them.

The first one is the issue of the rebate. So rebates in biological drugs now are around 50%, 45, 50% off the price of the drug in certain categories, anti-TNFs, insulins. And what happens is there's a list price, and if you're big buyer of the drug, you pay half the price as long as you've got the drug on a preferred tier. What happens is a biosimilar comes in, and you would actually want to move the old drug to the non-preferred tier and use the biosimilar as the preferred tier.

So I'll give you an example of a case where a list drug for the innovative drug is about \$10,000. It's obviously higher, but I'm just giving an example. Post-rebate, if you talk about 50% rebate, is \$5,000 per patient. Let's take a sample of 1,000 patients, a \$5 million cost for the payer. Now let's assume the payer wants to introduce a biosimilar.

Well, it's a \$10,000 price on the list price once you have taken away the preferred position of the innovator. It's still \$10,000. Let's assume you've got 500 patients still on the innovator drug. That will cost you now, since the price is twice, again, \$5 million. Now if the biosimilar developer even drops the price by 50% and the cost per patient on the biosimilar drug is \$500, that's an extra \$1 million. The total cost of acquisition of taking care of those 1,000 patients is now higher than it is to continue to use the innovator drug.

So, essentially, I speak to drug companies that [INAUDIBLE] they kind of mentioned as one of the tools in their portfolio is the level of rebate is essentially used as a barrier to adopting biosimilars. If you want to adopt a biosimilar, you must switch your entire patient population. If you grandfather existing patients in-- and existing patients are often 80% of the ongoing patient population every year-- you essentially have a barrier for adoption here that is quite material.

Second adoption is the issue of, where does the patient get its first dose? And once it's on that first dose, what happens next? So, for example, I've done some work on drugs that are being used in Medicare Part A. You've got a patient coming out of hospital. He's going to long term care. He's going to stay in long term care 200 days. And long term care providers are capitated for that period of 100 days.

They are highly incentivized to essentially pay less money for their drugs. The drug companies are highly incentivized to give the drugs to the long term care providers in Part A for a much lower price point. Why? Because then they capture the patient on their drug.

When the patient leaves long term care, goes back home, or just that period ends and he goes on a PDP program even in the long term care facility, he's now subject to another set of prices. The prices here might be a lot higher for the innovator drugs than for the biosimilar. But you would have to switch the patient from existing drug to a new drug, as opposed to a new patient start, which might be-- patient did not see either one of the drugs and the efficacy is presumed to be the same.

And we're seeing that right now with small molecules. Now, I'm just kind of giving two areas where I actually did some more work and I am somewhat more familiar with the details for small molecules. So, essentially, as one biological company told me, the price in the United States for a drug is also the lowest and the highest. Because the lowest price globally for our drug in the United States for some payers, which are the critical payers for us to be able to capture the patient. And obviously we charge less interested parties a lot more for the price of their drugs.

So, essentially, there are multiple barriers here that already exist in the system and multiple bugs simply because our system is very balkanized. There is no central planning of how we pay for drugs. Multiple organizations make decisions based on their own economic incentives. And the drug companies have been very, very smart in taking advantage of that.

I'm going to give you one more piece of data. And that is we ended up doing a lot of work on why small molecule drugs with moderate differentiation still do well. The FTC will probably be very familiar with the example of Nuvigil versus Provigil. The two drugs are very similar. You can think about this as a twice per day versus once per day drug or chewable drug versus a simple non-chewable drug.

And I was so surprised by the fact that those second generation of drugs despite very, very modest differentiation are able to maintain market sales despite the introduction of multiple generics of the first generation drug, which is only very different-- it's got only very small difference from the original drug. So I did a survey of managed care organizations, and the full

survey is actually in the back of this note, but the short answer is, if you ask them, why do you guys keep on covering those drugs that have very, very modest differentiation?

They acknowledge that it's not that those drugs are better. They deny that it's because they have an agency problem of their own, but they will basically tell you they have a major problem with drug companies being too smart and finding ways around the barriers they erect. And they have a problem with their own clients, the employers not quite willing or not quite understanding everything they need to understand to provide more pressure.

So we kind of look at biosimilars, which are clearly a new concept in medicine-- doctors are going to be less comfortable with them than with generics after 20 years. They're typically larger drugs and larger percentage of sales for the drug companies that are promoting them. And the same gaps, in my view, will be used prominently and even more so than in the small molecule world.

So the only comments I would have here for the regulators is please don't add any barriers to what biosimilar developers already have to contend with. Overall, frankly, I'm more optimistic because of these issue of-- we actually cannot afford to continue to have innovative medicine unless we find a way to cut the costs on the older drugs. Then over time we will have successive rounds of introductions, where over time we'll have faster and faster and more comprehensive adoption of biosimilars, but that adoption process can be 20 years or can be 10 or five. And right now, I'm tending to think more towards the latter end that's towards the earlier end. Thank you.

[APPLAUSE]