U.S. FOOD & DRUG ADMINISTRATION

THE HATCH-WAXMAN AMENDMENTS: ENSURING A BALANCE BETWEEN INNOVATION AND ACCESS

Keith Flanagan, Moderator

Office of Generic Drugs

Center for Drug Evaluation and Research

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Food and Drug Administration

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C O N T E N T S

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Elizabeth Dickinson,

Office of the Chief Counsel,

Office of the Commissioner, FDA

Keith Flanagan

Markus Meier,

Bureau of Competition,

Federal Trade Commission

Grail Sipes,

Office of Regulatory Policy, CDER, FDA

Peter Stein,

Office of New Drugs, CDER, FDA

Maryll Toufanian,

Office of Generic Drugs, CDER, FDA

Kathleen Uhl,

Office of Generic Drugs, CDER, FDA

P R O C E E D I N G S

MR. FLANAGAN: Good morning, and welcome. My name is Keith Flanagan. I'm the Director of the Office of Generic Drug Policy, in the Office of Generic Drugs, and I'll be serving as today's moderator. I'd like to thank you all, whether you're attending in person or watching via webcast, for joining our public meeting on the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access.

We're holding this meeting to provide an opportunity for the public to make your views known on how to maintain the balance between a steady pipeline of innovative drug development while speeding access to lower cost alternatives to innovator drugs. If you were unable to register in advance to speak today, you can share your view by submitting a written comment to the docket, which will remain open until September 18th. For your reference, the docket number is FDA-2017-N-3615. And the docket can be accessed at www.regulations.gov.

We have a full day today. Before getting

started, I'd like to briefly go over some logistics that will help keep the meeting running efficiently. As to logistics, if you haven't already done so please sign in at the registration desk, especially if you are presenting, so we can send any follow-up information after this meeting. Today's agenda includes a ten-minute break this morning, a one-hour lunch break, and a ten-minute break in the afternoon. We ask that you return promptly from the breaks and lunch, so that the 39 speakers are able to fully utilize their allotted time.

For any members of the media present, FDA press officer Sandy Walsh is available to help you. Sandy, please stand up and raise your hand to identify yourself. Please direct all media questions to Sandy. The Wi-Fi network name and password are available at the registration desk.

With respect to the agenda, the times listed on the agenda are approximate. If we finish one session ahead of schedule, we'll move right into the next part of the agenda. We'll try to end the meeting by 5:00.

Following our opening remarks and introduction of the panelists, we will have public presentations that represent the perspectives of those in academia and research, payers and providers, pharmaceutical product developers and patients and consumers. After each presentation, today, the panel will have an opportunity to ask questions. No participant may interrupt the presentation of another participant. Only the panel may ask questions after the presentations. I'll announce the first speaker of each set of speakers, but not each subsequent speaker. So, please approach the podium when the slide that lists your name and affiliation appears on the screen.

After presentations from the academic/researcher perspective, we'll take a ten-minute break. The payer/provider group will then present. Those presentations will be followed by lunch from noon to 1:00. After lunch are presentations from pharmaceutical product developers. Those presentations will be followed by the afternoon break, and then presentations from the patient/consumer perspective. I ask that each presenter remain at the podium after your

remarks, to allow the panel an opportunity for questions. After today's presentations, have concluded, I'll make brief closing remarks and adjourn the meeting.

Concerning the transcript and written comments, the record of this meeting will be transcribed. So, please remember to use the microphone when speaking. The transcript will be accessible through regulations.gov and the website for this public meeting in about 30 days. Any comments that aren't presented today can be submitted through regulations.gov using docket number, again, FDA-2017-N-3615.

And with that, I'd like to thank Commissioner Gottlieb for his leadership, activism and support, and invite him to make some opening remarks.

DR. GOTTLIEB: Thank you. Thank you all for coming today, and thank you for having me here. I want to discuss how we can make sure that, in places where Congress intended for there to be vigorous drug competition, such competition actually reaches the market. This is especially true as it relates to the

generic drug approval process, because generic medicines deliver so much value to consumers, and price competition to the marketplace.

The fact is that in too many places people can't afford the medicines that they need. Now, I know there are complex reasons for this. The structure of health insurance and formularies has changed, at times leaving some patients underinsured for the drugs they use. The pharmaceutical supply chain has also become more complex, and at times, more costly. A long series of middlemen sometimes extract premiums as drugs pass from manufacturers to patients, while adding uncertain value.

FDA doesn't have a direct role in how drugs are priced. But at FDA, we do play a key role, if indirect role, in the eventual cost of medicines. For one thing, our regulatory requirements impact the cost of drug development. On some level, drugs are ultimately priced to some measure of the cost of the capital needed to create them. These costs aren't just a reflection of the direct cost of drug development, but also the indirect costs. They include the cost of

scientific and regulatory risk. They also include the costs associated with the time it takes to develop a drug and gain its regulatory approval, and the costs associated with the research and development of experimental products that ultimately do not make it to market.

To the extent that FDA can make sure its own regulatory requirements are efficient, predictable, and science-based, we can also help reduce the time and uncertainty of drug development for both generic and branded drugs -- and ultimately impact the cost of these endeavors.

But there's another important way FDA can have an impact on drug costs. That's by encouraging competition. Consumers derive greater value when they have access to more choice and competition. This is especially true when it comes to new drug categories. Novel drugs that are therapeutically similar, or can be used interchangeably, can provide price competition. In other instances, they offer important clinical differentiation for patients who might not respond to one particular drug, but benefit from a medicine that

works through a slightly different mechanism.

The benefits of competition are equally obvious when it comes to generic drugs. But in some cases, we know that branded companies are using our rules that are intended to protect consumers, or meant to make the regulatory process more predictable, and taking advantage of these rules in order to deliberately forestall the entry of expected generic drug competition.

In other words, they're gaming our system. Let me give you some examples. In some cases, this takes the form of activities meant to make it hard for generic drug makers to physically purchase the branded drug that generic firms need in order to develop their own generic versions of these medicines. In other cases, it may take the form of raising scientific objections with us that are timed to maximize the potential for delaying the approval of a generic drug application. In other cases, it may take different forms entirely. This sort of gaming is wrong. It undermines the careful balance Congress struck between access and innovation.

We have a system that supports market-based pricing for innovation, as a way to provide proper incentives to entrepreneurs for taking on the uncertainty of these costly and high risk endeavors. But that means we also have to have a system that allows for vigorous competition once the patent and exclusivity rights have lapsed on these new inventions. This is the careful balance that Congress crafted when it created the modern generic drug framework in 1984. This careful compromise worked well for many years. We need to make sure it continues to support patients.

At FDA, we want to hear from the public today, about the ways we can continue to make sure that this system is benefiting consumers. We want to know how we can prevent a select few from disadvantaging many, by exploiting loopholes in our rules in ways that upset the careful balance between access and innovation. Ultimately, this sort of activity undermines the market-based incentives needed to attract the sort of entrepreneurship that supports new innovation.

It’s part of our public health mission to ensure access to safe and effective medicines. It’s

part of our public health mission to help make sure, within the scope of our legal authorities, that new technology can be more affordable. It's also part of our public health mission to address the gaming and abuse of our rules by a small number of actors bent on taking advantage of consumers.

We also need to make sure people can't use our approval process as another way to take advantage of consumers. In some cases, we've seen speculators purchase niche products that are not protected by patent or exclusivity but still face little competition, often because these drugs are infrequently used. These speculators then undertake very large and seemingly gratuitous price increases that appear untethered to any market condition or other practical consideration. They do this knowing that it can take years before another generic drug can enter the market to compete with them and force down their price. They're exploiting a regulatory arbitrage, born of the growing complexity of our regulatory system, and its occasional slowness.

We've already taken steps to address some of

these issues as part of our drug competition action plan. That plan has three major elements, each focused on places where I believe there are barriers to intended competition when it comes to the market entry of generic drugs.

Our goal, in each case, is to find ways we can adapt or change our own rules and practices, to make sure that in places where Congress intended for there to be vigorous competition -- and yes, lower prices -- these kinds of benefits are being realized on behalf of consumers.

So, let me tell you about the key components of our Drug Competition Plan, and some of the new steps that we're announcing today as part of this broader effort.

First, we're looking for places where this sort of gaming is happening, and we will change our rules where we can, to make sure that the competition that Congress envisioned is taking place. It's these sorts of scenarios that we hope to learn more about from this meeting today.

For example, we undertook an effort in 2014 to

facilitate access for generic drug applicants seeking quantities of branded drug products covered by REMS in order to perform the bioequivalence testing they need to do. We published a guidance that describes a procedure by which generic applicants can obtain a letter from FDA stating that their proposed study protocols contain sufficient protections such that the sale of the medicine to the generic applicant by the branded manufacturer would not be considered by FDA to be a violation of the branded drug's REMS.

In other words, FDA sends a letter to the company saying it's OK for the branded company to sell the drug to the generic manufacturer for these purposes. We're now taking a close look at that guidance and actively considering whether it achieves its goals or whether we could and should do more. One of the things we're considering is whether we make these letters from FDA publicly available, to make more widely known the instances where generic drug makers may be having trouble getting access to branded drugs. These letters could contain important information that can help inform the broader discussion about access and

competition. Their public release could be one-step to help ensure that unnecessary hurdles to generic drug development are removed.

Second, we're looking for places where the scientific and regulatory obstacles to the entry of generic medicines exist. In these cases, our aim is to address these obstacles by ensuring that our own regulatory processes are in line with the most current advances in science. We also are taking steps to further improve our scientific knowledge and enhance communication with product developers.

These obstacles can arise, for example, when it comes to complex drugs. In many cases, the traditional requirements used to demonstrate sameness may not be appropriate when it comes to complex drugs that can't be easily measured in the blood, or where the drug's therapeutic effect is delivered locally to a particular organ, rather than systemically, through the blood.

We've made significant progress on these fronts in the last few years. But we believe there continue to be additional steps we can take to improve

our own regulatory framework, to make it easier to demonstrate sameness in these settings, and to bring new generic competition to the market for complex drugs where relevant patents and exclusivities have lapsed.

And finally, we're going to be focusing on our own efficiency and throughput of the overall generic drug approval process, and the program. We need to make sure we are evaluating new generic applications in an efficient way, and making sure we keep the costs of filing generic applications low. By making sure the barriers to market entry are not unnecessarily inflated through the regulatory process, it helps keep costs low, and promote competition. So, we're taking new steps to build on the generic program's many successes and to continue to make sure its efficiency improves, and that our own review times continue to come down.

I want to close by describing some of these new efforts. The generic program has made substantial progress over the past several years. Thanks to the first generic drug user fee program, GDUFA I, beginning in 2012, FDA hired and trained more than 1,000 new staff, reorganized key offices, made significant

business process improvements, and we've also implemented a new Generic Drug Review information platform.

Last month, we fully approved 88 ANDAs and tentatively approved 12. That is a new record for full approvals in a month, breaking several other such records set since the start of GDUFA I. Working together, we're increasing the speed at which generic drugs can enter the market.

The biggest remaining challenge is that it has taken on average about four review cycles for an ANDA to reach approval. That's highly inefficient. It entails a greater deal of re-work by FDA and industry alike. It can needlessly delay consumer access to affordable medicines and raise costs.

The GDUFA II proposal, currently pending before Congress, is designed to reduce the number of review cycles for an ANDA to reach approval. It would expand the frequency and scope of communication between FDA and ANDA filers, giving applicants more opportunities to cure deficiencies and get ANDAs approved more quickly, including within their first

review cycle. It would also create a pre-ANDA program, with a special focus on complex generics. Applicants would obtain regulatory clarity earlier in product development, so they can submit ANDAs that are right the first time. Moreover, the program size envisioned under GDUFA II would be commensurate with the overall generic drug workload. Right-sizing the program will help us manage our workload and optimize resources for generic drug review and approval.

All of this is very good. But we can do more to build on the success that we have experienced in the generic program. So, we will be taking some additional steps I'd like to announce today.

By the end of this year, FDA will develop and issue two key documents to streamline the ANDA review program. First, we will issue a "Good ANDA Assessment Practices" MAPP. MAPP stands for Manual of Policies and Procedures. These documents are internal CDER policies that are posted on our website for transparency. This particular MAPP will outline ways that we intend to streamline the ANDA review process inside FDA, by, among other things, eliminating

unnecessary, duplicative procedures and greatly increasing the efficiency of our review.

This efficiency doesn't mean lowering our standards. In the United States, approximately 90 percent of the drugs that are dispensed are generics. That's because when consumers go the pharmacy, they can be confident that a generic drug will work the same as its branded equivalent.

FDA will continue to be the gold standard for review and approval of all drug applications, and we will make sure that consumers continue to trust that gold standard. It also doesn't mean altering GDUFA II review goals or program enhancements. One lesson that we learned from GDUFA and PDUFA alike is that truncating review prevents applicants from fixing their submissions and getting them approved. The result is additional review cycles, not faster approval. The goal of the MAPP is to help make sure that we work smarter.

The primary ANDA assessment should focus on "need to know" regulatory requirements. Supervisors should validate, not re-do, assessments. And the level

of supervisory scrutiny should vary according to the experience level of the primary reviewer and the risk and complexity of the product. At the end of the review cycle, if the ANDA is not approved, the complete response letter should clearly say what needs to be fixed. If the written communication is unclear, FDA should follow up and explain it over the phone in a direct, scientist-to-scientist exchange.

These improvements will increase efficiency and output, benefitting industry and consumers alike. These changes will also free up program staff to communicate more with applicants. It will also give us more time to engage in strategic, value-added policy and scientific initiatives. This includes, for example, initiatives concerning complex generics.

We hire and train talented, extremely dedicated staff to engage in critical thinking on behalf of the nation’s public health, not to administer unnecessary paperwork. I’m proud of the staff’s hard work and resilience, especially over the past five years. I’m strongly committed to supporting their work and enhancing their professional growth.

The MAPP and its related improvements are critical to the continued success of the generic drug program. However, at the end of the day, FDA can only approve submissions that are approvable. Industry must also do its part too, by submitting complete applications that are ready to be approved. Towards these ends, FDA will also issue a second key document. This ”Good ANDA Submission Practices” guidance will also issue by the end of this year. It will set forth common, recurring deficiencies that we see in applications, and provide advice on how these problems can be avoided in the first place, so applicants can send us ANDAs that are “right the first time”.

Neither our internal MAPP nor the guidance alone can ensure that ANDAs will be approved more efficiently. But taken together, I believe they will help effectuate real and measurable change. So, that's why I am delighted about these two new efforts. While we’re here to discuss the broader goals of Hatch-Waxman Amendments -- because at the heart of the law is an effort to ensure access to lifesaving medications. The efficiency of the review process is central to this

effort.

I'd like to close by thanking each of you for coming today. I'd also like to thank our staff for organizing and working to put this meeting together. My colleagues and I look forward to hearing from you today and considering your thoughts in connection with the drug competition action plan and our ongoing implementation of these efforts.

And I'd like to also close by taking this opportunity to introduce the next speaker, Dr. Janet Woodcock. I'm extremely grateful for the work that she has done, not just leading our drug program but also leading these initiatives, and extremely grateful and delighted to be back at FDA working with her again, and look forward to her remarks today. Thank you.

(Applause.)

DR. WOODCOCK: Thank you, Dr. Gottlieb, and good morning, everyone. Good to see you. Thank you for coming to this very important meeting. What we're talking about today is the balance set by Hatch-Waxman between innovation and access to affordable medicines, both of which are extremely important to the patients

in this country, as you know. And FDA's job is not to set that balance -- to decide where that balance lies -- but to preserve the balance that is established by Congress, and make sure that that weighing is actually instantiated out in the public. And part of the subject of this meeting is “have there been ways to actually subvert that balance, and actually tip it in one way or another not in favor of the public.”

We really here at FDA believe in innovation. And actually, I've spent a lot of my professional career trying to advance innovation by lowering the barriers to innovative products, through science, to improve the science of translational drug development and improve the success rate, actually, of innovations reaching the market.

FDA has a lot of expedited pathways, as you know, that are intended to help promising therapies get into the hands of doctors and patients as quickly as possible. And they include things like the breakthrough designation, fasttrack designation, accelerated approval, priority review, and so forth.

We also have worked over the past four or five

years to really enhance manufacturing and modernize manufacturing. And that's both in the innovator space and the generic space. And I think we're beginning to see the fruits of that. Actually, manufacturing, say, for a breakthrough drug, can be a tremendous delay in market access, due to the rapidity of development. And continuous manufacturing other newer technologies can actually overcome that barrier. So, there's a lot of work to do there, and we know that the newer products we're approving both can extend or save lives, or mitigate suffering in many cases. And so, patients are really depending on a robust pipeline of innovative products.

But at the same time, we don't want this to subvert the balance. And I think there's a fair balance there. Innovators can get rewarded for innovation. But at the same time, we can have a broad availability of affordable medicines.

Now, when you think about competition in the drug space there are really many paths to competition. The (b)(1) path itself we often approve additional drugs in a class. And although this is often

disparaged as "a me too" product, actually this can, in fact, introduce both choice and competition for consumers. In addition, in that area we have the (b)(2) -- the 505(b)(2) pathway, which can introduce micro innovations, so to speak -- not a new molecular entity, but some improved dosage form or route of administration and so forth, that can also provide both competition and choice for patients.

And now, under the generic program, with the success of GDUFA I, we have really stabilized and modernized the ANDA review program. This program was really the victim of its own success, and the rise of generics and the tremendous number of applications we began receiving had actually, five years ago, swamped the program. And we -- with GDUFA I, with the cooperation of industry and with Congress, this program has undergone deep and foundational restructuring to meet the current needs of the robust generic industry, that actually is sending in ever increasing number of generic drug applications every month, it seems like. Which is good news for consumers. And so, I'd really like to adjoin Dr. Gottlieb in congratulating the

staff, both in OGD, OPQ, and CDER and the staff in the field, ORA, all of whom really gave it their all over the past five years as the program underwent an amazing transformation that we've all -- we all worked just incredibly hard on. But, I think this program is really ready to deliver on the promise.

Now, at the same time there are new challenges, some of which have already been alluded to. We're working on things like chemical sameness for nontraditional kind of drugs -- for complex drugs. Drug device combinations are increasingly becoming the norm in some areas, and we need to figure out the standards for that in the ANDA world. And there are many other regulatory expectations that we need to work on. We also still have issues with labeling, that we hopefully will continue to improve our approach to that.

So, we also, a number of years ago, got authority to approve biosimilars. We just had an advisory committee this week where two biosimilars were discussed. And there have been significant legal policy and organization challenges to setting up this

new pathway, but I think this new pathway, which introduces competition for biological molecules, is established. We've had the first few approvals, but there are literally tens and tens of additional products under development over 50 programs going on, and I think we will see a flourishing of competition in this area as some of these begin to reach the market.

So, that's sort of the landscape of what we have. But, in addition to the issues that Dr. Gottlieb alluded to of gaming the Hatch-Waxman kind of balance that we have, the general issue of competition is one where FDA is just one piece of the puzzle. And, of course, drugs are distributed and marketed in the incredibly complex U.S. health care system, where it's not just complex distribution and so forth. The reimbursement situation is almost impossible, sometimes, to comprehend.

But, one of the things that we can't understand very well, and we'd like to hear input about, is what is the cause of so many of the market failures that we see where we don't see competition for either a single source innovator drug or a single

source generic drug. These lead to a lot of problems. They lead to shortages, where -- if you have a single source, where problems occur. Then we have a perhaps long-lasting drug shortage, sometimes of a lifesaving medicine. This is a terrible situation that the healthcare folks contact us constantly about.

Or, we see what Dr. Gottlieb alluded to, where we see price spikes of these sole source drugs, because getting competition onto the market takes a while. You have to have a plant, and you have to develop -- do some small studies, and submit an application. And this takes some time. So, we don't understand why when we may have robust competition at some time then the competitors will drop off. We do understand, and I've testified on this, that sometimes a month's supply of a generic drug costs a consumer less than a cup of coffee. Right. And there's something, you know -- I'm sure that's very satisfying for people who take a lot of drugs. That's very helpful for them. But, there may be some point where this -- is this one of the factors that's leading generic manufacturers to switch to a new line of

products, where they can get a higher reimbursement for. For example, new opportunities arise. The companies pursue them. They can't make everything. So, why are we losing competition?

It's unclear, also, the effect of mergers and acquisitions on competition, and how that is playing out. So, we have recently posted a list of off-patent off-exclusivity products with no approved generics. And if we get applications for those, we'll expedite them. But we realize there is an energy and cost and so forth that must go into developing a product and submitting an application for that product.

But, this is just a start of the conversation. I think you all collectively in this room, and hopefully on the webcast, there's much more diverse experience and knowledge about some of the root causes of this lack of competition, both the ability to delay entry of generics but also the problem of lack of competition in the marketplace.

And so, the purpose of this meeting is for us to hear from you, to a great extent, what the root causes are and what might be done about them so that we

can continue to maintain for the benefit of the patients of this country a proper balance between innovation on one hand and access to affordable drugs on another. Thank you very much, and look forward to your input. Thank you.

(Applause.)

MR. FLANAGAN: Now, I will introduce our panelists. The panelists are here to listen to the views of the public. They will be in listen only mode. However, they may ask clarifying questions following each presentation. Maryll Toufanian is Deputy Director of the Office of Generic Drug Policy in the Office of Generic Drugs.

I'd like to thank Markus Meier from the Federal Trade Commission (FTC) for joining us today. Markus is Acting Director of the Bureau of Competition at FTC, and I'll ask you to make some brief remarks after I introduce the rest of the panel.

Liz Dickinson is Senior Deputy Chief Counsel in the Office of the Commissioner. Dr. Peter Stein is Deputy Director of the Office of New Drugs. Dr. Cook Uhl is Director of the Office of Generic Drugs. Grail

Sipes is Director of CDER's Office of Regulatory Policy. And Anna Abram is Deputy Commissioner for Policy, Planning, Legislation and Analysis in the Office of the Commissioner.

I thank all of today's panelists for their participation. Now, Markus, if you have some opening remarks.

MR. MEIER: First, I'd like to say thanks, Keith, and thanks to the FDA for inviting me to be here. I'm a bit of the odd man out in this room. I'm certainly the odd man out on the panel, because I'm a law enforcer. I'm not a sector regulator. I'm not a policy maker. I work at the Federal Trade Commission, where we enforce the antitrust laws which are supposed to promote competition, one of the topics we're talking about today.

At the FTC, we're charged with promoting competition for the benefit of consumers. The laws we apply apply broadly across all sectors of the economy. They're not solely limited to pharmaceutical industry. I personally, however, happen to have worked on lots and lots of pharmaceutical cases over the years. I've

been doing it for about 27 years. And the way we try to enforce competition policy is by challenging certain types of business practices that might violate the antitrust laws, in the hope that by challenging those business practices we will actually promote competition -- the type of business practices we're concern about are things like price-fixing cartels, monopolization, and mergers and acquisitions that substantially lessen competition.

Now, one of the things that's very hard for people to understand, and something that we have to explain constantly at the FTC, is we don't have a federal law that goes against high prices. We don't have an anti-price gouging law. We don't have the power to just go after high prices for the sake of high prices. And in fact, if one really thinks about it it probably makes a fair amount of sense. As a famous judge in America, in a famous antitrust case once said -- and this is a bit of a paraphrase -- you can't ask people to run a race and then punish the winner for winning. If you want to have competition, sometimes there are winners and sometimes there are losers, and

sometimes people come out on top.

And I think when we think about this in the context of the pharmaceutical industry, it becomes even more important. We have a regulatory system that's designed to incentivize innovation through patents and through exclusivities, and one shouldn't be surprised when a company that has market power exercises that market power. And when you couple those issues together with the fact that there clearly are high barriers to entry into these industries, it gives companies a lot of market power. And when given that opportunity, they exercise the market power.

It's important to also point out that there is really limit on the ability for us to do our enforcement job. And some of these limits are that it takes a lot of time. So, we can never turn around something really quickly. Sorry, but we can't. It's often costly. And it's really uncertain, because we go through the courts. I have to be prepared, and my staff has to be prepared, to present cases in court and to win cases in court, and that can be very uncertain. So, let me give you one quick example, just for a

moment. I think most people in this room may have heard of pay for delay by now. These are agreements that branded companies enter with generic companies to settle patent litigation, and in that settlement the generic agrees to stay out for some period of time, despite the fact that they have final FDA approval to enter, and in return we allege that the branded company has made a payment to that generic company for that agreement to stay out.

Now, that seems to be pretty obviously anti-competitive. Yet, I personally have been working on this issue for 17 years, going on 18 now, together with a handful of other people who have been through it since the very, very beginning, in the late 1990s, and we got a great decision from the Supreme Court in 2013 and we're still fighting out these issues and we're still doing litigation all across America. This makes smart regulation and smart legislation imperative. And I think that's what we're really talking about here today.

I'd also like to say that the -- make sure everybody knows that the FTC and the FDA have enjoyed

for many years a really strong and good cooperative working relationship. We all know about Hatch-Waxman 1984, and we've all heard of drug substitution laws. But how many people in this room actually realize that states adopted drug substitution laws in large part because of an initiative by the Federal Trade Commission, working together with the FDA. Did a big report, did a big study, created a model state law that was adopted by many of the states across America -- and this was before Hatch-Waxman. So, just to give a sign of one thing that we can do together is that kind of work. We've obviously over the years done a lot of other collaboration and information sharing. And I think it's been a great relationship and I look forward to that relationship continuing to build and grow.

And then in sum, I want to say I'm really looking forward to hearing from the speakers today and learning additional ideas on ways that we can think about -- intelligently about these issues. Thank you very much.

(Applause.)

MR. FLANAGAN: It's now time to begin the

public presentations. We will start with the academic/researcher perspective. Again, I'll announce the first speaker, but not subsequent ones. So, please approach the podium when the slide that lists your name and affiliation appears on the screen. The first speaker is Michael Carrier, of Rutgers Law School.

MR. CARRIER: Thank you. My name is Michael Carrier. I'm a Distinguished Professor at Rutgers law School, and I'd like to present four proposals to enhance generic competition. This is an important exercise. Brand innovation has gotten a lot of attention. Generic access has not. I have comprehensively studied the issue as co-author of the leading treatise on IP and antitrust law. I've written more than 90 articles on IP and antitrust law, including 40 on pharmaceutical antitrust law. I've written many amicus briefs to courts on behalf of hundreds of professors, and I'm frequently cited in the media and courts, including the U.S. Supreme Court.

In a nutshell, the balance has tilted away from generic access. As Commissioner Gottlieb mentioned, Hatch-Waxman was all about a balance -- about brand

firm innovation as well as fostering generic competition. And brand firm innovation has been upheld. If you look at Hatch-Waxman, the mechanisms to promote brand firm innovation have been in effect. Things like patent term extensions, nonpatent market exclusivity, automatic 30 month stays -- there's no problem with any of that stuff.

On the other hand, generic competition has not always worked as meant to. So, if you look at the Hatch-Waxman Act, certainly there are a ton more generics than there were before. But, some of the provisions have been twisted far beyond how they were initially intended to be used. Start with the 180-day period of exclusivity. This was designed to promote challenges to invalid patents. Instead, it has been twisted so that the brand firm settles with the first-filing generic -- there's a rush to be the first-filing generic, because then you get paid to stay off the market. And so, this is the first way in which Hatch-Waxman has not worked as intended. There are easy fixes for that. Congress always thinks about or has legislation introduced that would open up the 180-day

period. So, it's not just the first filer who gets 180 days, but the first to win District Court litigation, or generics that are not sued -- let's have a race to be first to the market, rather than just a race to be the first filer.

In addition, REMS patents can be used to block generic competition. And so here, by just filing a patent in the Orange Book you get an automatic 30-month stay, but it seems like REMS patents are not the type of patents that should be listed in the Orange Book. They don't cover a drug or a method of using a drug. Rather, it's just a method of distribution. So, if you look at the REMS patents that have been listed, they don't seem to fall into the listable category -- the Xyrem patent dealt with a method of distribution using a central pharmacy. The Entereg patent dealt with providing hospitals with literature regarding the proper use of the drug. The thalidomide drugs dealt with the method of distributing a drug to avoid exposure to a fetus. These patents should not be listed in the Orange Book, and this is one potential thing that the FDA could do.

At the same time, these patents are not needed for innovation. Any time we hear about patents, we hear they're needed for innovation. This is a category that is not needed for innovation. For starters, after the Supreme Court decided the Alice case it's not clear that these patents are patentable anyway. The Court raised the bar significantly, and I don't think these patents would be awarded today.

In addition, my empirical study -- and this is all quoted in the slides -- found that of 60 NDAs covering REMS programs, only 5 were patented. And so, if brand firms have no problem patenting every aspect of the drug, the fact that they're not patenting the vast majority of elements of the REMS program shows that this is not crucial for innovation. And it's just one example of harm.

You look at Jazz Pharmaceuticals that argued against a waiver of the shared REMS program for generics that were utilizing multiple pharmacies. And the brand said, “Oh, you can't use multiple pharmacies.” Sure enough, there was a patent that covered a central pharmacy. So, the brand is saying

one thing to FDA in order to sweep the generics into the web of their patents.

Another way in which the balance is tilted away from generic access involves reformulations. Brand companies reformulate drugs all the time, and one empirical analysis several years ago, found that the vast majority do not present competitive concern. This study found that 80 percent of reformulations were done at a time that generic entry was not expected. And so,most of the reformulations are fine.

However, some are absolutely not fine. And the -- those that have been the subject of court cases have been those that make no economic sense at all, other than harming generic competition. So, why would in the Namenda case the brand firm pull a $1.5 billion drug off the market? Makes no sense. Why would, in the Suboxone case, the brand company disparage its own drug -- say there are safety concerns with its own drug, but then leave its drug on the market for another six months. Why in the Doryx case and the Tricor case do we have the brand company destroying its own inventory, changing the code to obsolete in the

database. This makes no sense at all, other than harming generic entry. So, in short, even though the vast majority of reformulations are fine, there are some that are a perversion of the state substitution laws, of the Hatch-Waxman Act, where the change is made only to stifle generic entry.

The fourth category involves citizen petitions. I have conducted two empirical studies of citizen petitions. In 2011, I looked at every petition filed between 2001 and 2010, and I found that the FDA denied 81 percent of these petitions. Last year, I updated my study, looking at every 505(q) petition. Those are the most concerning ones. They target a pending generic. Looking at all of those between 2011 and 2015, and I found that the FDA denied 92 percent of these petitions.

I then parsed it even more closely, to look at the types of petitions that showed the even greater concern. And so, there are some petitions that are late filed, within six months of the expiration of a patent or data exclusivity period. The FDA denied 98 percent -- 49 out of 50 of these petitions. And then

there are the simultaneous petitions. Those were the FDA makes a decision on the petition at the same time -- either same day or, extrapolating further, same month -- that the ANDA is approved. And 100 percent of those petitions were denied, when there was a simultaneous determination. So, in short, the figures are very concerning.

Then you look at actual examples. Those are even worse. So, the FTC filed its first case challenging citizen petitions against Shire ViroPharma, which had 46 regulatory and court filings. Teva had multiple petitions on the Copaxone drug. Bayer filed a petition against Mirena one day before patent expiration. And then the EpiPen has gotten a lot of attention for price increases, but there is a citizen petition angle there as well in which you have a delayed petition coming on the heels of the settlement that it entered into which delayed competition even further.

So, in short, there is a real tilt away from generic access. What can the FDA do? Well, I have four proposals. The first is to clarify the Orange

Book listing. It seems like REMS patents are not drugs or methods of using drugs. Rather, they're just how the product is distributed. This is a really simple fix. You look at 23 C.F.R. § 314.53(b)(1). You have certain categories there, that cannot be listed -- process patents, packaging, metabolites, intermediates. Just add REMS to that list, and it will be perfectly clear that you do not get an automatic 30-month stay from filing this thing that has nothing to do with innovation, that is just done to block generic entry.

My second proposal is a little more complicated, because here we have shared REMS negotiations. And here you don't have an on/off switch, at which the brand's refusal to negotiate automatically becomes something that is anticompetitive. In day one it's not. In year 15, it is. But what's the point in which it triggers over that line. We don't know. But we have seen certain examples where there has been delay, where the brands have slow-walked negotiations -- and I mention the Suboxone, the Xyrem case as potential examples. In Suboxone, for example, the FDA contemplated a quick

development of a shared REMS program, given that the brand already had a REMS that was there and all you had to do was add the generics. But, according to the plaintiffs in that case, the brand turned down numerous invitations to participate in meetings, refused to share information until its demands were met, and refused to cooperate until the generic gave the brand a veto or supermajority power.

So, what can the FDA do given this slow-walking of negotiations? For starters, the FDA could more quickly allow waiver. In theory, it's great to have shared REMS programs but in practice it's better to get the generic on the market. And when the brand is using the shared REMS process in order just to delay the generic from entering the market, perhaps we could be quicker to allow waiver. Relatedly, there could be expectations discussed during a kickoff meeting, in which it's made clear what the norms are and how the waiver would be granted. Additionally, the FDA could develop guidance on when the burden outweighs the benefit, and therefore a waiver would be allowed.

So, we could look at things like the number of

ANDA applicants. As the number of applicants increases, we would expect the process to take a longer time. The complexity of the ETASU restrictions -- if we're talking about a complex restriction, like a distribution restriction, we should expect more time than a simpler restriction, something like patient or physician enrollment. The potential delay in generic approval is something else to look at, and finally perhaps a history of unsuccessful negotiations could lead to a quicker waiver. Again, all of these shedding guidance on the factors that will be considered in granting a waiver.

In addition, we could think about templates that would shoehorn part of the process, or at least short-circuit it, by which the brand would make clear upfront what it would accept in terms of governance terms, NDAs, IP licenses, diligence, indemnity and insurance.

And finally, perhaps even think about a time frame. The CREATES Act, being considered in Congress, set a 120-day period. That's something to think about as well.

Before I get to proposal 3, perhaps I could offer proposal 2-A, based on something that Commissioner Gottlieb said in his introductory remarks. And that is making these letters publicly available in the REMS process. And so, the thought was that we -- if we have these letters, then they would give the consolation to brands that they wouldn't be on the hook. The letters have not been used in that way. The brand company basically throws the letter in the trash, in some of these cases, and says thanks but no thanks. And so, in the Cornell Law Review article that I have forthcoming that I quote on the previous slide, on page 49, note 370, I give examples of how the brand company ignores the letter.

And so, in the In Re Thalidomide and Revlimid case, the Court talked about that. In the Actelion case, the brand company said it would sell to the generic if it got a letter. And then it got the letter and said, quote, this changes nothing, you still don't get the sample. And so, if the letter really does mean nothing, when the brand company will always say forget the letter, I still have safety concerns, then let's

make the letters publicly available. Let's shed some more light on this issue.

To proposal 3, we can loosen the distribution restriction bottleneck. The statute says that REMS should not be used to block or delay generics. But, that is how REMS have been used. And so here, these are changes that Congress could make. Perhaps the FDA could support them in the first one with block or delay, make clear that a patent is not a defense here. In the second one, where we talk about shared REMS, let's remove patents as an excuse for switching to a waiver, just because that is not needed for all the reasons I've mentioned before.

Along similar lines, you could do what was done in the America Invents Act, with tax-strategy patents. Those were not the strongest patents in the world. You could something similar with REMS patents, and say that they constitute prior art and therefore should not be able to be patented.

The final proposal is to address the harms from citizen petitions. And so, here I would start off by saying that the FDA should include a

comprehensive list of 505(q) petitions in its annual report to Congress. There is a report every year. It includes some information, but there is a ton of information that researchers like myself and others would really find useful. So, as someone who has gone through all the citizen petitions, there is no simple answer to where we find the information. For my first study, I went to regulations.gov. That's really difficult to navigate.

For my second study, I had the benefit of Kurt Karst at FDA law blog that collects every citizen petition. It overlaps with regulations.gov, so it makes my life a lot easier. But why should we be relying on Kurt? As great as his work is, this is something that FDA has access to. Let's see a list of every citizen petition. That would be very helpful. In addition, let's see the timing of the petition in relation to the patents in the Orange Book. How much time was spent on each of these petitions, and how much delay was caused by the petitioning. So, in these reports it says, well, there's been almost no delay -- there were only nine petitions that were delayed

between fiscal year 2008 and 2015, and my sense is delay there is determined by something that goes beyond the initially 180, now 150, day period. But that seems to be too strict a definition. It seems like there still can be delay, even in the 150-day period. So, maybe FDA does decide within 150 days, but the ANDA is delayed because the FDA is dealing with a frivolous citizen petition that takes an extra 100 days within the 150-day period. So, let's get information on that sort of situation.

The second proposal here is to focus on summary disposition under 505(q)(1)(E). So, FDA in theory has the power to use summary disposition. As far as I can tell, it has not used that power. Something is not right there. The standard seems to be pretty high, when you say that there has to be a primary purpose of delay as well as not on its face raising valid scientific or regulatory issues.

For starters, how do we show a primary purpose of delay? A lot of these petitions are frivolous. But you can't tell that in an instant, by looking at it. And you can never figure out the primary purpose of the

brand company when it's doing these things. And so, the standard seems to be too high. I would think about getting rid of the primary purpose of delay standard, and then focusing on whether or not this is an appropriate standard. Yes, I certainly see the concern with summarily disposing of one of these, and then having it come back to bite you later on if there really is a safety concern. But on the other hand, if you do have this power and it's never been used, what good is it actually doing.

The next issue deals with simultaneous determinations. So, again, getting to the point of delay, it's possible that with all of these determinations when an ANDA is approved at the same time that a 505(q) petition is denied that it's possible that the ANDA approval was delayed because you were dealing with the petition. And if that's the case, then that would be something that would be useful to know.

We don't know. There's no transparency as to the timing of all this. That would be very helpful. Some others have raised concerns that maybe the

announcement of the FDA's decision was delayed under ANDA approval -- if you delay that announcement on the petition's denial, then you forestall a court challenge until the ANDA is approved. And so, that's something as well. Again, we don't see from the outside. So, that's something that can be clarified.

The next point is how much time and money was incurred in resolving these petitions. In the annual reports, it talks about this. Let's see. This is not a costless exercise. Yes, there's a freedom of speech and a right to submit petitions. But as a practical matter, these are wasted resources. Let's figure out how much money and time that could raise the political will to do something about the process.

And finally, the 505(q) in terms of the certification of objections needs to be within a reasonable time. So, in the EpiPen case this was years after they were aware of the ANDA. Something is not right there.

In conclusion, not one thing I have said would rebut or get in the way of legitimately issued patents. Not one thing I said would get in the way of

innovation. These are evasions of the system. This is an evasion of the regulatory regime. And there's no good reason at all, especially in all the citizen petitions and REMS aspects that I talked about, that FDA can do something about -- this is not about innovation. It's about consumers getting the right to generic drugs that they have every right to get. Thank you so much for your attention to this crucial issue.

(Applause.)

MR. FLANAGAN: Thank you, very much. Any questions from the panel?

MS. DICKINSON: So, Mr. Carrier, thank you. I have one question. You did pose the challenge of product hopping, and abandoning what are apparently viable products for alternative products. But, you didn't pose a solution to that particular matter. Is that because solutions fall outside FDA's authority?

MR. CARRIER: So, it's difficult when a drug is just a little bit different than the earlier drug what FDA could do. And so, one thing that FDA could do, which could be a very aggressive change, would be to raise the standard when you have a me-too drug.

Should something get FDA approval when it's basically the same thing as the old one, you're just adding a second score or you're going from 50 milligrams to 100 milligrams or something like that. That would deal with changing the standard for review. And so, that would be one thing to think about. But, I recognize that that is a bit of an aggressive approach.

DR. UHL: I appreciate your presentation this morning. And although some of your recommendations are obviously legislative, or regulatory, none of which are rapid, I want to follow, though, on Liz's point. Because that really struck me, this aspect of reformulation. Are there ways that you can suggest that FDA should be able to target or identify these formulation changes prospectively, so that we can target this product hopping? I believe most of your analysis was, obviously, retrospective. It's kind of easy to tell when it product hopped after the fact. It's less easy when it's in the midst of a supplement at the agency under review. So, do you have any guidance or suggestions to us how to prospectively identify that 20 percent for which you say are

problematic?

MR. CARRIER: So, perhaps we look at the markets. When you have very large markets, like for cholesterol drugs, it seems like there are a lot of changes that are made that are not the most revolutionary in the world. And so, perhaps a dosage change or a formulation change -- I recognize some of these might be legitimate, but perhaps the changes that are less significant are worth more attention. So, I would say where you have a large market -- where you have something that's far away from the active ingredient, dealing with something that is very small in nature, like a dosage change or a line on a drug that would allow it to be split, or something like that, that would be something that would seem to deal less with innovation.

MR. FLANAGAN: Any other questions from the panel? Thank you.

MR. CARRIER: Thank you.

DR. SARPATWARI: Good morning. Hi. My name is Ameet Sarpatwari, and I'm the Assistant Director of the Program on Regulation, Therapeutics and Law at the

Department of Medicine at Brigham and Women's Hospital and Harvard Medical School. I appreciate the opportunity to present comments at this meeting. So, I want to just quickly, in terms of summarizing my presentation, give three respective ways problems in which generic drug availability is hampered and generic drug usage is hampered, and what possible solutions could be.

So, just by way of background, between 2014 and 2016, net retail prices increased 10 percent annually. These were driven by higher launch prices and markups on existing brand-name drugs. These brand-new drugs enjoy extensive market exclusivity. If you're talking about widely used drugs you're talking about 12.5 years; first-in-class drugs 14.5 years. And the fact of the matter is that these price increases are having a substantial impact on patients. 20 percent of 2,001 respondents in a 2016 survey did not fill a prescription in the past year due to cost.

So, the gravity and the importance of timely access to generic drugs and promoting generic drug usage is important. And yet, it is being hampered, and

one of the reasons is restrictive distribution networks and REMS. So, restricted distribution networks in which you have a single specialty pharmacy or multiple certified pharmacies, which can be independent or part of REMS, companies have been exploiting in a way that -- in a way to deny generic drug access for bioequivalence testing. So, the FDA has testified last year that it received 150 inquiries from generic manufacturers unable to obtain brand-name samples necessary for bioequivalence testing.

In addition to the component of access to samples, there's the component of REMS with regards to the patenting and shared REMS with elements to assure safe use. So, that includes patenting REMS and also refusing to engage in meaningful discussions in which to have shared REMS. In addition, you have 11th hour citizen petitions -- so, citizen petitions are mechanisms that allow individuals, including companies, to request that the FDA take or refrain from taking an administrative action.

Between 2000 and 2012, 40 percent of citizen petitions pertaining to generic drug -- pending generic

drug applications, were filed within a year of generic entry. If we take a further look between 2011 and 2015, of the 124 citizen petitions pertaining to pending generic drug applications, 87 percent were by brand-name manufacturers, and only 8 percent were granted. In one egregious case, you had a company filing 24 citizen petitions to delay generic vancomycin. And so, the FDA has stated that citizen petitions delayed five generic drug approvals between 2013 and 2015.

I think it's important to also stress that we need to be focused not just on timely availability of generic drugs, but on timely usage of generic drugs. And we can't ignore the problem that there still is lingering skepticism about generic drugs -- safety and effectiveness. And part of that is the fact that you have $24 billion of pharmaceutical marketing to physicians. Now, that was in 2012, so obviously that number has increased. About a third of physicians and patients still harbor some generic drug skepticism, and there is still a sizable way to go in terms of achieving optimal both bioequivalent and therapeutic

substitution levels.

So, with regards to those problems, what can we do? First, in terms of curbing restrictive distribution and REMS misuse, I think the FDA can compel sample deposit as a condition of drug approval. So, for instance, compelling at least enough samples being deposited as a condition of drug approval sufficient to have bioequivalent testing done by three generic manufacturers, and then conditioning receipt of those samples for bioequivalence testing on a commitment to market the product for a minimum period of time -- say, for example, five years -- and on the condition, that if that drug has -- is a REMS covered drug, that you have a receipt of FDA safety certification for the testing.

I think from a legislative standpoint a fix is needed, and that fix is the CREATES Act, which would authorize generic manufacturers to petition a court to require sale of drug samples if a brand-name manufacturer blocked access. It would mandate FDA safety certification for REMS covered drugs, and it would allow FDA to require shared programs or approve

separate REMS.

Separately, you could -- in terms of a patenting issue, I think you could request Congress to prohibit REMS patenting or, as Professor Carrier has recently argued, to at least go to the extent that was done in the America Invents Act to say that patenting REMS would be -- would not meet the prior art standard. So, in addition to that you could request Congress to require government owned and operated REMS. I've recently been doing a series of interviews with stakeholders about physicians and patients with their experiences with REMS, and one point that physicians repeatedly made is why companies were running REMS, why it wasn't the government actually in charge of running these programs.

In terms of combating citizen petitions, a lot of these petitions stem over complex generic products. And so, providing early guidance early on on showing bioequivalence for these complex drugs is important. And in order to do that, and in order to promulgate that guidance, you could levy user fees to conduct necessary research and involve brand-name manufacturers

early in that province, in terms of the guidance development.

In terms of this notion of still having these manufacturers promote citizen petitions as a delaying tactic, perhaps the FDA could adopt a rebuttable presumption of delay for late-filled citizen petitions, and presume that brand-name manufacturer petitions pertaining to generic applications filed less than nine months before the expiry of the primary patent on the brand-name drug is a delaying tactic, which would require a preliminary finding that the petition would likely be granted based on compelling evidence in order to proceed to a full review.

And finally, in terms of promoting evidence-based decision-making and increasing physician confidence and patient confidence in generic drugs, I think it's important that the FDA continue to use Sentinel to conduct generic drug safety surveillance to support comparative safety and effectiveness research and dissemination, and that this could be to recommend that Congress specifically earmark funds from PDUFA for this purpose, and recommend that the Department of

Justice earmark a proportion of, let's say, off-label settlements for this activity.

In terms of addressing deficiencies in generic direct labeling, I think it's important to issue annual reports on generic drug safety and label changes and create a central online repository of dynamic labels so that physicians and patients have an easy to access record. And in terms of stemming confusion about what generic drugs are or whether or not they are somehow inferior or different than brand-name drugs, requiring generic drugs to have the same appearance as brand-name versions is one possible additional step.

So, thank you.

(Applause.)

DR. SARPATWARI: Happy to take any questions.

MS. TOUFANIAN: Thank you for your comments. I have two -- a two-part question related to the skepticism concern that you referenced in your presentation. The first is in your research, have you identified specific therapeutic classes for which the skepticism of the healthcare practitioner or the patients is particularly high? And my second question

relates to your last comment requiring generic drugs to have the same brand version as -- excuse me, have the same appearance as the brand-name version. If you have data to support that as a particular concern.

DR. SARPATWARI: Sure. So, in terms of specific classes of drugs we do know that in particular -- at least, our research has shown that for narrow therapeutic index drugs there is a particular concern. And we know specifically -- at least have -- are building a body of evidence in terms of which physicians and which patients are more skeptical. So, targeted interventions with relationship to those particular drugs to those populations is a viable solution, in terms of increasing confidence overall.

As to the second question, I'm happy to share with the group studies as to the decrease in adherence as a result of a shifting pill color appearance -- and so, size or shape, color -- and what the impacts are in terms of patients stopping taking their medication. And so, ultimately, it's that balanced with -- you do hear generic companies say that if that change were to result, it would result in an increased cost of

production. But, you've got to weigh that against the potential increase in adherence that would result from patients being less confused about their medications.

DR. UHL: If you have particular data, could you please submit that to the docket? That would be very helpful to us.

DR. SARPATWARI: I'd be happy to. Thank you.

DR. UHL: Thank you.

MR. MEIER: Okay. So, when I made my remarks about the FTC I described us as a law enforcer. But, we also have a unique aspect to our constitution, all the way back to the 1914 -- when we were created, Congress also gave us the right to do research and original projects like that. And we've used those authorities quite a bit, in fact, in the healthcare area, where we've done a number of studies over the years. So, we have some unique tools, including the ability to subpoena companies and those kind of things. As a researcher, yourself, what research would you prioritize if you were in charge at the FTC?

DR. SARPATWARI: Oh, boy. That's a -- you're asking a million-dollar question. And I am

particularly concerned right now -- at the FTC, you said.

MR. MEIER: Yes.

DR. SARPATWARI: Yeah, okay. I would be particularly interested right now in how the PTAB process may be facilitating pay for delay settlements, that may hindering timely availability to generic drugs, as one possible concern. And I would be interested in further studying the anticompetitive effects of restricting -- of these restricted distribution pathways, in particular. Those would be two areas.

DR. UHL: In follow-up to your question -- I mean, to your comments about promotion and skepticism, and you mentioned the extent of pharmaceutical marketing, and et cetera, that's typically brand-name pharmaceutical marketing. So, do you have any recommendations or suggestions to the generic drug industry with respect to that?

DR. SARPATWARI: So, I mean, part of the magic of generic drugs is that they don't engage in that marketing, and thus those costs aren't going to be

incorporated into the cost of the generic product. So, it's a difficult position for generic manufacturers to be in. But, I think it's important to capitalize on what existing research has been done in terms of how to persuade physicians and how to show value to physicians. And I think that there are scalability issues with regard to things like academic detailing that generic manufacturers should actively investigate, to see that even if they can't compete on the same level, in terms of the amount of promotion that's going on, can they maximize the way in which they will put out evidence that physicians and patients can use to make more informed choices.

MS. SIPES: I had a quick question pertaining to your suggestion -- one of your suggestions about citizen petitions. You talked about on the second bullet there the potential to require a preliminary finding in some cases that the petition will likely be granted, based on compelling evidence, in order to proceed to a full review. Can you say a little bit more about that, or maybe give an example of how that might play out in terms of degree of review of the

actual evidence?

DR. SARPATWARI: Sure. So, in the case that I think other scholars have mentioned, that there are certain citizen petitions in which the substance of the information presented does not really make -- it is fairly apparent that this is a delaying tactic and not really a substantive question of safety or efficacy, that those are questions that could potentially be weeded out in a preliminary review. And there are -- there's -- in the same way that you can get granted a preliminary injunction, at a federal district court or something of the sort, where the court is decided to consider the likelihood of prevailing on the merits, this would be a sort of similar way to weed out some of those petitions to actually lessen the workload of actually undertaking a full review. So, if that were a possibility, I think that that could at least maximize the resources that the FDA had and make sure that they're not being spent on citizen petitions that really don't warrant that much of resources.

MS. SIPES: I do hear what you're saying, but I'm -- I guess I'm trying to dig in a little more, and

sort of get a sense of what the circumstances would be in which this kind of preliminary finding would be made. I mean, when is it apparent that full review is not necessary, I guess is what I'm asking.

DR. SARPATWARI: So, there I think that you could have -- and I -- you could convene a body of experts who have significant experience with these petitions. And actually, entrust them to make those decisions based on expertise. And in terms of if you're specifically asking what would be the reasoning behind making those decisions -- so, I want to just make sure I'm understanding.

MS. SIPES: I -- clearly, it would take, you know, expertise to make these determinations. And I guess this is a -- you've largely answered my question, I think, in terms of your thinking. I guess it's just that it's -- the degree of review of evidence that it would -- that would be necessary to make this kind of determination is not, kind of, I think immediately clear.

DR. SARPATWARI: Yes. And so, the question is it really is a matter of considering how many of

those citizen petitions that would undertake a rigorous review -- how many of them could actually be on a more superficial review, be cut out of the process. And that's an empirical question which I honestly don't have the answer to. Thank you.

MR. BRILL: Good morning. My name is Alex Brill. I am a Research Fellow at the American Enterprise Institute, and I'm also Principal at a consulting firm, Matrix Global Advisors. I'm speaking this morning on my own behalf. These views expressed are mine and only mine, although I have provided counsel to both brand and generic drug manufacturers in the past.

I thank you for having this meeting today. This is perhaps one of the most important topics in pharmacoeconomics, this striking of the balance. It's also one of the hardest questions for economists and policy makers to wrestle with. I'll try to be brief in the next few minutes, and not be redundant to comments that were made earlier, all of which were appreciated.

I'll start with my key point, and then make a few specific policy suggestions and observations. And

the key observation that I wanted to convey this morning is that the objectives laid forth in this meeting, the balance between innovation and access -- or, as I would suggestion, innovation and competition -- is not a zero-sum game. But in fact, policies that are intended at encouraging competition can also be positive for innovation. In other words, innovation does not always come at the cost of access, and competition does not always come at the cost of innovation.

This can be illustrated simply by looking outside the pharmaceutical space and thinking about the phones that each of us are carrying. Samsung is spurring Apple, and the Samsung Galaxy is spurring the iPhone, to innovate. The threat of that -- those competitive pressures on each other is pushing forward the technology in that industry, and leading to better outcomes. Similarly, the threat of generic entry or entry of a competing brand can also spur innovation in the pharmaceutical industry. This isn't always necessarily the case, as was mentioned earlier. Sometimes those innovations or changes can be small, a

product hopping or evergreening. But, it does have the potential to have a strong and positive innovative effect through more competition.

It's tempting, I think, to look at the parties in front of you in a dispute -- a brand versus a generic -- and think of this in a sense as a zero-sum game. And it is, of course, a game of winners and losers in any particular challenge. But the proper framework, I think, is one of a welfare perspective -- not about the two manufacturers that are seeking an advantage over another, but rather of the customers -- the consumers. And whether those consumers may be consumers seeking the advantages of a new and innovative product, or those consumers may be seeking the advantages of a more cost-effective product.

And the other large point I want to make is simply that the marketplace is increasingly sophisticated here. The Hatch-Waxman Amendments that date back to the mid-1980s were enacted at a time where, quite frankly, the industry was different, both with respect to the generic industry as well as with respect to the brand industry. And so, it's

appropriate to consider and reevaluate where these balances may lie.

Let me also just touch -- and this was also mentioned in the opening remarks -- when we think about competition, we tend to think about them in the very simple and -- manner of the competition between the brand and the generic-- the generic entry as being the quintessential example of competition in the pharmaceutical industry. But in fact, I think there are four straightforward and obvious types of competition; three of them are related to the subject at hand. Brand to generic, the one I just mentioned.

Generic to generic competition is also critically important. Simply, it's not a binary choice that -- in the marketplace that there either is or is not generic entry for a given product, but in fact more generic entrants result in different market dynamics. And we know that in part due to some research from the FTC.

And brand to brand competition, which was also mentioned in the opening remarks. Brands can -- although not always, can compete with one another.

Brands in the same drug class can compete with one another on price.

And the fourth part would be the biologic/biosimilar competition dynamics. Most economists consider this dynamic or expect this dynamic to be similar to that in the brand to brand space, in some respects, although perhaps it will be its own unique dynamic, but, of course, outside the Hatch-Waxman framework.

Thinking a little bit more specifically about a few policies to consider, one that's been discussed by the last two speakers, and I won't rehash these remarks, but the restrictions that are imposed through the use of REMS with ETASU and REMS-like programs that block generic competition in my view is certainly not something that was intended by Congress, and that does upset some of the balance between competition and innovation.

In work that I did earlier this year, I tried to get an estimate -- admittedly, an upperbound -- on the scope and scale of this marketplace, identifying over 70 drugs with over $20 billion in annual sales

that are potentially at risk of restrictions. And work that I did back in 2014, looking at a sample of 40 products which there had been evidence of restricted access, tried to estimate the potential lost savings, at over $5 billion a year economy-wide and almost $2 billion a year to the federal government. This is an issue not only of potential foregone savings in the healthcare space, but one that will alter the balance between innovation and competition.

Also, as Dr. Janet Woodcock mentioned in her opening remarks, there are many brand products for which there are no exclusivities or pending -- or patent protections, yet no generic approval. I think it would be misleading to think that we'll ever see generic competition for all of these products. There are natural market forces that may prohibit a generic entry. But, I also would believe that an exclusivity for the generics can be a positive policy change that could encourage more entry of generics into this space. And we saw in legislation passed by the House of Representatives last week, I believe, that a policy in this vein is likely to generate additional cost

savings, which suggests to me that it is likely to generate additional generic competition.

With respect to the generic to generic competition dynamic that I mentioned a moment ago, this too is very important to think about. It's not -- we should not think of this as simply a binary choice, but rather we should be encouraging not only generic entry, but robust generic competition. And the evidence presented in Reiffen and Ward research that started at the FTC clearly illustrates the importance of more generic entrants into a market for driving down costs.

And then finally, the important brand to brand competition. And again, I'll reiterate that brands do not necessarily always compete on price with one another. But they can. And that in the given -- the current framework that we have, where we -- where the FDA prioritizes -- expedites various approval pathways -- given the fact that there's resource constraint at the agency, the additional emphasis on these expedited pathways necessarily means, I think, that there are more limited resources available for these "me too" products. But, these me-too products can also be

procompetitive in many respects.

And I'm out of time, so that just details my earlier comments.

MR. FLANAGAN: Thank you. For you -- how would exclusivity for generics for sole source markets incentivize product development, since there are no competitors to exclude?

MR. BRILL: I think in the current landscape, absent that incentive, generic manufacturers may hesitate to enter out of fear that a competitor is similarly engaged in the same process. And so, it's about -- a bit of a prisoner's dilemma, in a sense. Two generics both -- either one willing to enter, but fearful that the other one is entering simultaneously.

MS. DICKINSON: You mentioned that there have been a number of changes in the marketplace and in the industry since 1984. Are there particular developments that are salient for the agency's implementation of the statute that you would direct us to?

MR. BRILL: Just in the broadest terms, we see both very high share of the market captured by generics. Nearly 90 percent of all prescriptions are

generic prescriptions. And we see the generics can capture large market shares relatively quickly, particularly for large product classes. On the other hand, on the innovative side, as we all know we see prices for brand products at launch significantly higher than they had been historically, even adjusting for overall inflation and other dynamics. So, the pull is in both directions. How it nets out, it's hard to speculate.

MS. TOUFANIAN: Thank you. On your second to last slide, you noted that there's a lack of a sufficient number of ANDAs to maximize the competitive market dynamic. I would surmise that some of that is attributed to the pay for delay settlements that Markus is interested in. But, in addition, are there other market forces that inform generic drug entry when there is no legal impediment that intersects with FDA's regulatory space in a way that FDA could look at more closely.

MR. BRILL: I'm sorry, you're referring to multiple generics in a space, or generics when there is no generic?

MS. TOUFANIAN: When there are less than the number of generics that you identified. We know that some are precluded from entering into the market due to the exclusivity of those first applicants. In other scenarios, we may have seven, eight, ten generics approved and yet only two are marketing at any given time.

MR. BRILL: Yeah. So, some of it is what I would call natural to the market. For small products -- for small product classes, the market can only withstand a relatively small number of competitors. And so, we shouldn't always expect the five, six number of generics in a market. It depends on the particulars. But, in other cases there could be regulatory barriers. And I can't say with certainty, but we should think of the application process as a hurdle for entry.

And to the extent that those hurdles -- and they're barriers, in other words, and to the extent that there are costs associated with those, whether the direct literal cost or the time and risk associated are large, that will deter generic competition. And in

particular, it will deter additional generic competition in these smaller products. And so, for, you know, a billion-dollar product firms would be happy to shell out a few million dollars for an ANDA. As the products get smaller, those hurdles and burdens become potentially more binding.

DR. STEIN: The point you had made with regard to brand to brand competition, and the need to have more within a class for stimulating competition, did you have specific suggestions? You commented on the approval pathways for breakthrough medications, priority review. Specific suggestions for how FDA would address this issue?

MR. BRILL: To be honest, I think it's a true challenge. Many of these expedited pathways are legislated. There's a political desire, and a reasonable and appropriate one, to direct resources into certain types of pathways to unmet needs, which is an appropriate and reasonable area for which the agency should be working diligently, and is. But it comes at that cost. And so, you know, in the simplest terms additional resources -- or, at least, an awareness of -

- within the agency of how resources may be -- are perhaps being diverted to the expedited pathways that are set by Congress, at the expense of standard reviews.

MS. ABRAM: Going back to your evergreening comments, are there specific examples of types of evergreening that you believe are disrupting the balance that Hatch-Waxman sought to strike?

MR. BRILL: No. I think that we -- again, it's more of a scientific question, I think, and outside my scope of expertise. The -- this question of what is a significant change versus what is an incremental change is extremely difficult for policy makers, and certainly difficult for those who are -- of us who are not from the hard sciences, to wrestle with. I think, though -- I would note that some of this issue could be -- some of the burden here should not be attributed solely to the agency, and that the industry -- and that the marketplace itself can potentially resolve some of these challenges. And what I mean here is that the payers should be aware of the differences in products, and how those products are tiered and

whatnot can influence the outcomes at the end of the day as well.

DR. UHL: I just want to follow up on the question from Peter, about the brand to brand. Do you have particular examples that you could provide us where the -- that demonstrate the -- your second bullet here, the expense of approving brand products that offer the opportunity to compete directly. Are there particular circumstances or examples of product development meetings that didn't happen, IND meetings that didn't happen, NDAs by which we missed goal dates, or whatever? I just -- I think it would be -- I intuitively understand your point. But do you have data to substantiate that?

MR. BRILL: I think it's virtually impossible measure empirically. And I don't have -- if I had an anecdote, I would share it. I'm not close enough to the process to be able to share an anecdote. But empirically, to demonstrate this -- a meeting that would have happened or something -- the but for cases is hard to imagine. I think it is -- as you said, it's intuitive in the sense that given the fact that there

is a fixed amount of resources that are available, and there is a pull on those resources into a particular direction, that necessarily means that there can be other activities that lag. The extent to which this is a concern, or empirically, I think would be very difficult to measure. Perhaps it's measurable internally. But even then, I think there would be challenges. Okay. Thank you.

DR. POLLI: Good morning. My name is James Polli. I'm a faculty member of the University of Maryland. I'd like to talk with you about pharmaceutical quality. Pharmaceutical quality is a -- I have some slides. Yeah. Okay. So, in any event, pharmaceutical quality is an area where Hatch-Waxman Amendments have had a favorable impact on the development of both brand and generic products. Pharmaceutical quality is an interest to all pharmaceutical companies throughout entire product lifecycles. I intended to show a schematic of how pharmaceutical quality is designed into products, with time progressing from the beginning of development to subsequent development.

Innovators learn about formulation risks and sensitivities during development, often through failures. When development efforts are successful, product formulation, manufacturing and quality control tests are arrived at as clinical development proceeds, even after phase 3 studies are completed. There is a reliance on the bioequivalence standard during innovator development. A typical NDA has four to six bioequivalent studies. After NDA approval, CMC experts remain busy throughout subsequent product lifecycle stages. After patent expiration, generics enter the market employing the same bioequivalence standard.

The notion and availability of generics has brought about a public interest in and public discourse of pharmaceutical product quality. Questions include who, where and how is medication made. What nondrug ingredients go into the medication, and what is their impact. What quality control tests are used, and what do they assure. What is the bioequivalence standard and is it good? Is this the same product that was made last month? Is this a narrow therapeutic index drug? These are not always easy questions, particularly for

drugs that are difficult to formulate and for complex formulations. Innovator companies have substantially contributed to pharmaceutical science that underpins the answers to these questions.

However, there is little doubt that Hatch-Waxman has had the effect of greater public interest in and public discourse of pharmaceutical product quality, which has benefited everyone, including both innovator and generic companies.

FDA-sponsored research to examine pharmaceutical quality and manufacturing standards. I have two examples -- actually, maybe I don't. This first example is a study designed to address questions from pharmaceutical scientists, from both innovator and generic companies. We examined whether large amounts of common excipients impact bioequivalence for so-called BCS Class III drugs. Excipients are nondrug ingredients in medicines, like fillers and binders, and are typically present in quantities larger than the drug itself. We found that a dozen of the most common tablet and capsule excipients do not impact bioequivalence.

So, we've developed a list of common excipients that we concluded that need not exhibit qualitative and quantitative sameness between pre-and post-change products, including brand and generic, for tablets and capsules. Hence, human testing is not necessary to bioequivalence of BCS Class III drugs involving these excipient changes. FDA has since provided regulatory relief. Innovator and generic companies are utilizing these new guidelines. In 2010, we had conservatively estimated that such regulatory relief would directly save $62 to $71 million each year.

A second example is a study designed to address concerns from neurologist and epilepsy patients. The American Epilepsy Society was opposed to generic substitution, since it had questions about the bioequivalence standard, which is typically performed in healthy volunteers and not in patients. Neurologists were most concerned about the anti-epileptic drug lamotrigine. We performed a switching bioequivalent study of the brand lamotrigine and the most common generic in patients with epilepsy under

clinical conditions. We've published this work, where one can see that bioequivalence was observed.

A second similar study showed bioequivalence between two generics. Last year, the American Epilepsy Society rescinded its 2007 position statement that opposed generic substitution, indicating "These studies confirm that the U.S. FDA standards for bioequivalence are appropriate for patients with epilepsy."

Again, Hatch-Waxman Amendments have had a favorable impact on the development of both brand and generic products through greater public interest in and public discourse of pharmaceutical product quality.

MR. FLANAGAN: Sorry we disrupted your flow. Your very excellent slides will be part of the public record.

DR. POLLI: Okay. All right.

DR. UHL: Jim, thank you very much. Are you making the recommendation to us that that list of common excipients -- if there's a product that includes that list of excipients, that we waive bioequivalence? Or are you making different recommendations?

DR. POLLI: No, I don’t think I have anything

to add beyond what we have already published. Which is more -- which provides more relief than what I understand the current -- what the agency currently does. Just through -- I was just really saying that through competition there's been a greater focus on pharmaceutical quality, and that has elevated the game of all formulation scientists throughout the world, regardless of who their employer is.

And in that one particular case that you're asking about, it sort of inspired questions about, well, what should the standard be, is there ways to relax the standard, should it be tightened. So, I think that sunshine has been helpful in this space. It's also -- I would also say that it's also helpful in that it's also helped recognize that some products are in fact more complex than others. So, it's just a sunshine issue.

MR. FLANAGAN: Thank you.

DR. BERNDT: Good morning. My name is Ernst Berndt. I'm a Professor at MIT. I'd like to speak today about some recent research results. If you could -- the research is our own. It's sponsored by the NIH,

and it's joint with a professor at the University of Chicago named Rena Conti, and my postdoctoral fellow, Steve Murphy. Two more slides down, please -- or no, I -- oh, here we go.

The research I'll talk about this morning is not yet published. It's currently being submitted as working papers to the National Bureau of Economic Research. We expect they will be available publicly in a few weeks.

I'll talk about two study questions. One is how competitive are product markets in the U.S. generic industry, how do we quantify that, and what are trends in that over time. And the second thing I want to talk about is to what extent has GDUFA, the first authorization of the Generic Drug User Fee Act, exacerbated certain concentration trends and hindered competition in the generic drug industry.

Let me just start by defining what we mean by a product market. This is an important issue in antitrust economics. What I'm going to do here is define a product market by the combination of the active pharmaceutical ingredient and the root of

administration. That is to say, if we take a drug like -- brand-name drug like Pepcid, which is famotidine, oral versions -- all oral strengths of famotidine and Pepcid would be in the same product market. However, injectable would be a different product market. And similarly, ranitidine, which is Zantac, would be in a different product market than Pepcid. The data that we use is for 12 years. It was from QuintilesIMS, and it's through all drug channels, not just the retail channel. Let me skip ahead here. There are four regulatory regimes we distinguish. One is pre-MMA. That's before passage of the MMA implementation -- before implementation. After 2006 until the beginning of 2010 is we call the MMA era. That's MMA was implemented. Then passage of the Affordable Care Act in the second quarter of 2010, until third quarter of 2012. And finally, the GDUFA era, which was after GDUFA was implemented, which is beginning in the fourth quarter of calendar year 2012 -- not fiscal year, calendar year.

What we do is rather conventional, in terms of methodology. There's no real innovation here. What

makes the study quite useful, I think, is the level of detail -- very disaggregated -- by product market.

Let me start, then, with revenues. On the vertical axis, here we have revenues in thousands of dollars per quarter. We have time on the horizontal axis. And what we do is we do the interquartile range and the mean. That is to say, if you look at the very bottom line there that tells us that 25 percent of these product markets have quarterly sales of $100 million or less. That's $400 million per year. If you look at the red line just above that flat line on the bottom, that's the median revenues. What the median revenues are at the beginning of the samples are around 150 -- sorry, about $100 million per quarter, and at the end of the sample it's up to about $150 million per quarter. So, rather quite a small market. If we look, however, at the mean -- which is way up on top -- we see that means are very, very much larger than even the 75th percentile, suggesting that there's a very small number of very large revenue drugs. Probably authorized generics, or perhaps even some branded generics. But, for the most part I think it's

important to characterize this industry as consisting of a lot of products that have small revenues.

A second thing to look at is entry and exit. The -- what we define as an entrance is a product for which for two quarters -- at least for the last two quarters there's been zero sales, zero units sold. And then we see positive thereafter. That's called an entrance. And an exit is when we don't see any product sales in revenues, dollars or in units, for two quarters. What you see here is on the top you have two lines. One is the absolute number, and on the right vertical axis a percent -- 1, 2, 3 and 4 percent. What you see, therefore, in the top is that over time, for the most part, there's been more entry than there's been exit. The top two lines. And that the total churn rate is about 5 percent a quarter. What you also see is that towards the end of the sample, on the right-hand side, you see that there's a convergence between entry and exits.

Following passage of GDUFA, the entrance rate actually fell. I'm not attributing it, necessarily, to GDUFA. There may be many other things going on, like

patent cliffs and things like that, and consolidation. But you also see the number of exits increasing quite substantially towards the end of the sample.

How many manufacturers are there in a typical product market? What this tells you is that for the most part the median there is between two and three. It means that 50 percent of all generic product markets have two to three competitors, no more. The 75th percentile is the line on the top, which says between five and six. The mean here is between four and five. So, what this tells you basically is that most generic markets not only are small revenue markets, but they have a small number of competitors. So, they're highly concentrated.

This is probably the most important slide of this set, and this is -- let's take a look at all these product markets, and see how many of them have only one competitor, only one ANDA actively being marketed, how many have two, how many have three and how many have four or more. What you see here is a couple of things. One is the lines are all pretty flat. So, this is a steady state sort of thing. This is not abrupt

changes. They're pretty flat lines. But, what you see, for example, is that blue line on top says 40 percent of all generic markets have only one supplier. Dr. Gottlieb's data from the other day talked about the number that have no generics at all. We're looking at just those markets where there is a generic, and 40 percent of those markets have only one supplier. Another 12 to 15 percent have two suppliers. So, that means that more than half of all markets have two or fewer suppliers. On the other hand, there's about 40 percent that have four or more suppliers.

I won't present regression results here, other than to show that during -- if you look at what happens to exit rates, you see that during the GDUFA era they are higher than in the pre-MMA era, and that they're higher typically for orals than they are for injectables or other routes of administration. If you look at entry shares, you see the opposite happening. Whereas there's increased exit over time, there's decreased entry. And the entry -- the decreased entry is particularly notable amongst injectables. This is a slide that looks at what happens to the price per

standard unit in QuintilesIMS parlance, as a function of how many competitors are there. And as you'd expect, the larger the number of competitors the lower the price, other things equal. And they find an elasticity here that's about -.75, and it's robust to how you measure the number of competitors. In other words, whether they use a corporation or a manufacturer count.

So, three takeaways from that. First is the quarterly sales revenue for a manufacturer/molecule are surprisingly small. Generics product markets generally have a small number of competitors. Median is two. And while there's -- entry was outnumbering exits through most of the sample, since 2013 these churn rates have converged to one another. Could reflect many things -- patent cliff, consolidations, barriers to entry and inducements to exit from GDUFA I.

Okay. One comment that's more of an economics sort of issue, in this country we have legislation that called Hart-Scott-Rodino legislation, which requires any merger and acquisition that exceeds some threshold to be publicly reported so it can be scrutinized by the

DOJ or the FTC. That current threshold is $81 million. Given how small the revenues are for a lot of these generic manufacturers, that tells us that there can be mergers and exits, and that would not exceed the Hart-Rodino threshold but could still be very important in terms of public health, for making the concentration even higher and supply more vulnerable.

Let me just comment for a few minutes on GDUFA and PDUFA. And I mean -- by PDUFA, I mean, the Prescription Drug User Fee Act for brands that was originally implemented in 1992, and GDUFA will be the one from 2012, whose authorization is now being considered. Similar to PDUFA, GDUFA had a one-time application fee. But GDUFA had annual facility fees, that were larger for fixed final dosage forms than for API -- actual pharmaceutical ingredient -- facilities, and it was $15,000 larger for a foreign than for a domestic applicant.

In PDUFA, there were no foreign domestic distinctions. And annual establishment fees but not annual facility fees. Because of importance of contract manufacturing, primarily in the generic drug

industry, but not as much, apparently, in the brand-name drug industry -- although there is some there -- GDUFA had a one-time drug master file fee that ANDAs could reference, but there wasn't a separate contract manufacturing organization fee from facility fee. And there's no analog to that in PDUFA.

Quite importantly, unlike for PDUFA, with GDUFA, the annual facility fees were due at the time the ANDA was submitted, rather than after the ANDA was approved. For PDUFA, the annual establishment fees are not assessed until the product is actually approved. What this means, then, is for those generic manufacturers having a backlog, which for a while was as much as 48 months -- that means for those four years you have to pay facility fees even though you don't have a product on the market. Okay. I might note that GDUFA II plans to address that issue, and I'll talk about that in a minute. But, in terms of just seeing how large are these fees, here are the various fees of one-time ANDA fees, product -- prior approval supplement fees and drug master file are all in the $35,000 to $70,000 range. The annual program fees are

quite a bit higher. If you look at the final two columns, for a final dosage form, it's -- domestic it's $258,000 at the end of the sample, and for foreign it's $15,000 more, at $274,000. And I might note, so that generic manufacturer submitting an ANDA, with having to wait for years, has to pay $1 million during that interval before it has any revenues. That discourages entry.

I might also note that the growth rates of all these fees are considerably higher than the growth rate of prescription drug prices. So, what did GDUFA do to try and address this. One thing that the FDA noticed, and industry agreed with, was that the revenues were highly volatile -- how could they be made more predictable. And here an important change, I think, is that the -- instead of assessing them annually on the stock of approved ANDAs, they'll now be addressed on the -- sorry, instead of addressing on the flow of new ANDAs, they're now going to be assessed on the stock of all approved ANDAs, which is a much more stable and predictable number. And the supplement fees are entirely abandoned.

Finally, there are some small business concerns. There will now be an annual program fee for -- that will depend on how many ANDAs is held by a firm and its affiliates. For small ANDA holders -- that is, from one to five ANDAs -- they will have a 10 percent of the full fee assigned. For medium -- that is, holding a portfolio of 6 to 19 ANDAs -- that will be a 40 percent of a full fee, and then the full fee would be for those that have a portfolio of 20 or more ANDAs.

The FDA estimated that in 2016, there were about 10,000 approved ANDAs, but they also recognize that there were a lot of ANDAs that were not being marketed anymore. And so, part of the issue of the whole GDUFA funding IT support, and so forth, and enabling the FDA to monitor the industry was to try and find out more carefully just how many of these products are actually being marketed.

The actions that the FDA took was to use the Orange Book to identify the apparent ANDA owners, ask them as of November 14th, to inform the FDA by February what ANDAs they owned and whether they were being manufactured and marketed. Only 7 percent of the

identified ANDA holders responded to that request. However, they were very disproportionately large ANDA holders. The average portfolio size of a respondent to that was about 15 ANDAs, but some of them were much, much larger. For example, Teva holds, as of that date, 1,609 ANDAs; Mylan, 662; Novartis, 647; and then, a fair number as well. Ten largest of those responders claimed 70 percent of all the claimed ANDAs.

Why do I raise this issue? Well, Dr. Gottlieb proposed recently that there would be expedited review for all those markets in which -- for any ANDAs submitted in a market in which there were three or fewer ANDA holders. By our count here, that's 60 some percent of all markets. It's not a very discriminating sort of tool. It's a very -- and most of those markets are probably extremely small, and the reason they're small is probably because they're very, very old drugs, for the most part. Now, some of those very old drugs are very important -- standard of care. But many are not, and there's probably good reason why they're obsolete. We've got some better products now in turn to address those needs. But, what -- the point

we want to make here is that the FDA could burden itself enormously if it had to do expedited review of 60 percent of all ANDA holders -- of all product markets. Now, the -- it's very unlikely that there will be that many applicants. But this suggests to us that there might be a more focused way of trying to find what are those product markets which have very few competitors, but are really important, in terms of the public health. How that would be done I don't know. There may be room for patient advocacy groups here, for rare disease orphan drug groups, or there may just be other ways in which the economists at the FDA can collaborate with their medical staff colleagues on identifying what those markets are.

Thank you.

DR. UHL: Thank you very much. In your earlier slides, with the analysis of entry and exit --

DR. BERNDT: Yes.

DR. UHL: -- where -- because you looked at, if I recall correctly, 2004 to 2016.

DR. BERNDT: '16.

DR. UHL: So, over that 12-year period, did

your analysis also take into effect the mergers and acquisitions? Because there were a substantial number of mergers and acquisitions during that time period.

DR. BERNDT: The way in which the QuintilesIMS data handles mergers and acquisitions is rather tricky, in the sense that they always attribute the manufacturer as combined when postmerger. So, we didn't explicitly look at the role of consolidation and M&A activity. But, we do very much expect, and from press releases we're led to believe that a lot of M&A activity resulted in the closing of redundant plants. The -- I might add that the number of API and final dosage form facilities has actually declined quite a lot -- by about 20 percent. So, it's not just a -- some products exiting. It's actually plants exiting as well.

DR. UHL: So, did you do anything in your analysis to control for that?

DR. BERNDT: Not yet.

DR. UHL: Okay. Thank you.

DR. BERNDT: We hope to do that soon.

MR. FLANAGAN: Thank you.

DR. BERNDT: Thank you.

MS. SIPES: I'm sorry. I'm so sorry. I actually had a question. Sorry about that. Thank you very much for this presentation. I'm just wondering -- I see your point in the second part of the presentation about the impact of fees on entry and exit. Did your work lead you to any other insights into factors that strongly affect generic entry and exit beyond the fee structure, in terms of what companies look at when they make their decisions?

DR. BERNDT: Well, we do know as well that for very good reason is the FDA increased its monitoring of both domestic and foreign manufacturing sites, for quality control and sterile manufacturing, things like that. And we have noticed that a number of firms withdrew their products after getting their Form 483 complaints. So, it's not just GDUFA. It's other regulatory activities, which are very important to maintain so that we have an assurance of high quality manufacturing. But, that probably -- again, because some of these markets are so very small, with small revenues, the cost implications of upgrading so that

you're up to date with current good manufacturing practices can be quite substantial, and can lead to exit that way as well.

In the academic literature on generic drugs, we've studied very, very closely the first 24 months after loss of exclusivity, but we haven't really looked at what happens to mature markets. And there's not been much work at all on factors affecting the exits.

So, I -- the answer to your -- long answer to your short question is that there is some work on this, but very little has been done. And I think it would be an important area to follow up on.

MS. SIPES: Thank you.

MR. FLANAGAN: Thank you. Now we'll take a ten-minute break, which means we'll return at 11:13 and kick off right then. There's a kiosk serving coffee in the lobby. Restrooms and vending machines are out there. If you'd like to preorder lunch, you can do so at the kiosk.

(Off the record at 11:03 a.m.)

(On the record at 11:16 a.m.)

MR. FLANAGAN: As with previous presentations,

I'll announce the first speaker but not subsequent ones. So please approach the podium when the slide that lists your name and affiliation appears on the screen. And after your remarks, please remain at the podium to allow the panel an opportunity for questions. Sir.

MR. EBERT: Thank you. And good morning, and than you for the opportunity to be here today and to give our perspective on increasing access and competition in the generic drug market. And thank you to the FDA for its leadership on this critical issue. My name is Todd Ebert. I'm a registered pharmacist. I'm a former CEO of one of the nation's leading GPOs, and I am now currently the President and CEO of the Healthcare Supply Chain Association, HSCA. I have no slides today. Our comments have been submitted in more detail to the docket.

HSCA represents the nation's leading health group purchasing organizations, or GPOs. GPOs are the sourcing and purchasing partners to virtually every hospital in the country, as well as the vast majority of long-term care facilities, surgery centers, home healthcare providers and clinics. We help healthcare

providers leverage their purchasing volume to negotiate competitive prices on their healthcare products and services, which lowers costs for patients, providers, payers, Medicare and Medicaid, and taxpayers. GPOs deliver the cost savings that allow providers to focus on their core mission, providing first-class care to their patients.

Given the unique line of sight that GPOs have over all aspects of the healthcare supply chain, HSCA submits for your consideration the following administrative and policy solutions that we believe will help lower costs and increase competition and innovation in the healthcare market. It is important to note that much of the information that I'll share with you comes from our customers -- our members and the customers they serve, the pharmacists out in the field.

Generic drug shortages and price spikes. Price spikes are commonly used generic drugs -- price spikes for commonly used generic drugs and ongoing prescription drug shortages are jeopardizing patient access to care. As you know, generic drug price spikes

often occur when a lack of competition among drug manufacturers allows high prices to go unchecked. Research and experience indicates that the introduction of at least one competitor reduces drug prices, but only modestly. But when there are at least three competitors, the price drops precipitously by more than 40 percent. Increased competition engenders even more favorable drug pricing for consumers and providers. We applaud the FDA's recent action to increase generic drug competition by giving priority review approval -- priority review to abbreviated new drug applications for which there are three or fewer alternatives.

HSCA also supports your recent action. We also support similar legislative efforts, including S.1115, the Making Pharmaceutical Markets More Competitive Act, a bipartisan piece of legislation from Senators Collins, Franken, McCaskill and Cotton. The language drawn from this bill is in the most recent Senate draft of the User Fee reauthorization bill, and similar language was included in the House version, which unanimously passed on the House floor last week.

As the FDA takes additional steps to further

increase competition, we suggest that you consider implementing more specific timelines for these expedited reviews. Generic injectable drugs are the workhorses of acute care facilities, and shortages of these drugs create significant challenges for patients and providers alike. Shortages are often exacerbated by the backlog of ANDAs at the FDA, which can delay product review for up to four years -- product delay and introduction. To help resolve these issues, we recommend that the FDA utilize its current authority to fast-track applications for generic injectable drugs as well.

Working closely with manufacturers to maintain a supply of generic medications. The nature of generic injectable drugs requires rigorously-maintained manufacturing processes. Manufacturers of these drugs sometimes shut down plants or specific lines for FDA-mandated CGMP improvements or 483 observations, even in instances where only small issues need improvement or where the remaining areas are functioning successfully. These shutdowns can lead to price spikes and to shortages for drugs ranging from saline to chemotherapy

treatments. We believe that improved coordination between divisions at the FDA, as well as more rapid review of manufacturer corrective actions, would help to moderate supply and price fluctuations for these drugs.

Pay for delay tactics. HSCA opposes so-called pay for delay tactics. Tactics are the practice by which some brand-name pharmaceutical manufacturers attempt to pay the manufacturer of generic drug alternatives to not to enter the market. Pay for delay can give rise to lack of market competition and delay patient access to cheaper alternatives, and we urge the FDA to take action within its authority to end this practice.

Now, as noted by Alex Brill, biosimilar products were -- aren't part of Hatch-Waxman. But, this is something we feel very strongly about, and that is the biosimilar nomenclature. HSCA is also concerned about the impact on competition of the FDA's rule on biosimilar nomenclature. Current FDA guidelines call for a unique four-digit suffix for biosimilar names. We are concerned that an arbitrary suffix may lead to

clinician confusion and hinder the adoption of biosimilars. We encourage the FDA to eliminate the four-digit suffix to help promote competition and eliminate possibility of confusion for clinicians and patients.

In conclusion, I would like again to thank the FDA for allowing us to provide our perspectives and recommendations today. HSCA looks forward to continuing to serve as a resource to the FDA for the FDA to continue working with the agency to increase generic drug competition.

Thank you.

DR. UHL: Thank you for your comments. I have two questions, based upon some of your recommendations. One was if we could implement more specific timelines. Do you have a recommendation to us about what that would look like?

MR. EBERT: Yes. Eight months.

DR. UHL: Eight months. As opposed to ten months, the standard GDUFA.

MR. EBERT: Right.

DR. UHL: Okay.

MR. EBERT: We are supporting the legislation by the Senators, S.1115, which calls for eight months.

DR. UHL: Okay. That would be for which specific kind of products?

MR. EBERT: These would be for the generic products in the express lane. Those that had three or fewer manufacturers.

DR. UHL: Three or fewer.

MR. EBERT: Uh-huh.

DR. UHL: Okay. And then another comment that you made is to fasttrack generic injectables. Is that a recommendation to fasttrack all generic injectables, or specific injectables?

MR. EBERT: Only those in which there is limited competition, and where there are opportunities or there's something out in the queue that is waiting to be reviewed and approved, that they would receive a fasttrack.

DR. UHL: And what do you mean by fasttrack? Do you mean --

MR. EBERT: Meaning that they --

DR. UHL: -- the same thing as the specific -

- the other specific timelines?

MR. EBERT: Yes, ma'am.

DR. UHL: Okay. Thank you.

MR. EBERT: Thank you.

MR. RUSSELL: Good morning. My name is Wayne Russell. I'm the Vice President of Pharmacy for Premier, Incorporated. Premier is a healthcare alliance, serves approximately 3,700 hospitals in the United States and about 130,000 other provider organizations in the nonacute markets. We're a leading healthcare improvement company. We unite the alliance of hospitals and other providers to lead the transformation of high quality cost-effective healthcare.

A key component of our alliance is our pharmacy program, which combines clinical data with purchasing power to deliver reduced costs, improve quality and safety and increase knowledge sharing amongst healthcare professionals. I am responsible for a team in Charlotte, North Carolina, that contracts with major manufacturers in the pharmaceutical industry, including both brand and generic

manufacturers, distributors, wholesalers, pharmacy technology suppliers, service companies, plasma drive products, vaccines and biosimilars. We have sourcing committees made up of clinical experts from our member hospitals, who also assist us in the evaluation of current emerging pharmaceuticals for contracting and patient care.

Because of the disparity in the FDA approval standards between 1938 and 1962, Congress required that drugs approved in the time frame be reviewed again for updated safety and efficacy requirements. The FDA carries out these requirements through a process called drug efficacy study implementation, or DESI. While the FDA's efforts to obtain safety and efficacy data on all drugs in the marketplace is laudable, many of these drugs have a long history of safety and efficacy. Because of the length of time they've been on the market, and also the competitive nature of many of these drugs and number of manufacturers that were making them, most of these products had relatively low prices.

Premier recommends several things for the FDA

to consider in changing the process to allow more notice for manufacturers and providers regarding the FDA action on these older drugs when immediate removal from the market we consider to be not necessary. First, we recommend that the FDA announce in the federal register the first NDA approval for an older medication currently manufactured by several companies. Second, we recommend that the FDA allow 18 to 24 months after that notice before requiring the current manufacturers to exit the market. This would give providers, purchasers and consumers time to engage with manufacturers on their decision-making regarding seeking FDA approval of a drug that is under this designation. Third, if a manufacturer already has an application at the agency, they should not be required to leave the market when the other manufacturers are instructed to do so.

The disruption to the marketplace when other products are required to exit as a result of the FDA's policies should not be underestimated. When manufacturers of these older drugs leave the market -- examples include guaifenesin, levothyroxine, digoxin,

morphine, colchicine -- providers have experienced significant drug price increases due to the lack of competition, and in some cases, it's created drug shortages.

I have several slides that show examples of what I'm talking about. This is an example of potassium chloride, which in 2014 sold for approximately $40.86 for a 20 milliequivalent per 15 ML liquid product. When other manufacturers were required to leave the market, the price jumped to $236.93 in 2016. Epinephrine -- which, by the way, is currently on the drug shortage list -- sold of $69.16 a vial in 2015. It jumped 352 percent, to $312.50, in 2016 -- one year -- when other manufacturers were required to leave the market. The price has continued to go up another 20 percent this year, on a drug that's been in the market with no new indications or therapy improvement for many years. As you know, again, this is a drug on the drug shortage list. The third example is norepinephrine. This drug was priced at $33 for ten vials in 2009. When the brand Bloxiverz was approved by the FDA -- same package size -- it jumped to $150 in

2013. It continued to go up to $938.12 in 2015, and then you'll see that there were two other products -- two other manufacturers that came onto the market and the drug now has dropped down to about $580. But again, the point being that it started out at $33 and now it's at $580. So, there's still a significant increase in price, even though we now have three suppliers.

So, again, on behalf of our hospitals, physicians and patients, we request that the FDA seriously reconsider the administration of this program and its impact it's having on cost of care and product availability. Thank you.

MS. TOUFANIAN: Thank you for your comments. Could you give a little bit more detail on the benefit that you see resulting from permitting those products who are not approved to market within the 18 to 24-month period you described?

MR. RUSSELL: Well, these are products that would be currently on the market, that the FDA has targeted to take out of the market. So, it's not like they haven't been around for many, many years. The

benefit would be it would give organizations like myself and the hospitals and physician community that I represent time to talk to manufacturers to see if somebody is going to remain in the market, submit an NDA or ANDA, or everybody is going to exit the market.

The other dynamic that it would allow us to do is talk to the manufacturer that theoretically has filed the NDA, is going to stay in the market, and quite honestly determine can they supply the market. That's a real problem we have today. Epinephrine is a great example. The manufacturer that stayed in the market couldn't supply the demand that existed in the market, when all the vial manufacturers got out of the market, and then we had a problem with quality for a syringe manufacturer of that product. So, now we have a drug shortage. So, we have price escalation and a drug shortage to deal with, of a very critical drug.

DR. STEIN: So, one issue I'd be interested in your comments on -- the process is intended to allow us to assure the quality of the product that's approved by going through the application and the approval process. How do you figure that into the

considerations? Obviously, there's value in having as much competition in the market as there can be. But how do we fold in the consideration of the product quality that we can assure through the application process with the importance also of assuring competition in the market?

MR. RUSSELL: We're not saying that we should subvert that process. We're not saying that that process that exists shouldn't be ignored. All we're saying is that there needs to be consideration for -- and due time given for when manufacturers are told to exit the market because, basically, data on a drug that could be 50 or 60 years old, and been in the market for 50 or 60 years, hasn't gone through the process that exists today. So, we're not saying do away with that. We're saying give everyone time to make some determinations.

Number one, if somebody did file an NDA and go through the expense and the data process, can they supply the market yes or no. That's something that organizations like mine are very uniquely able to establish, and we would welcome the communication with

the FDA to determine that thing.

Secondly, we know who other suppliers are in the market of those products. I assume the FDA does too. We could have conversations with them. We could encourage them to stay in the market, and hopefully lead to a market, given some adequate time, where everybody understands what's about to happen -- that we would still have two or three or four competitors, not just one. Or maybe none. Okay.

MR. EITING: Good morning. My name is Paul Eiting, and I'm the Senior Manager of Value-Based Policy at Blue Cross Blue Shield Association (BCBSA). I'm happy to be here. I have oral comments, but I do not have slides today. So, as many of you know, BCBSA represents 36 independent and locally based plans providing coverage to over 106 million Americans. And I'm here presenting the opinions of the association on the topic today.

First, we applaud the FDA's launch of its Drug Competition Action Plan, as mentioned today by the Commissioner, and efforts to remove barriers of competition to generics. We look forward to learning

more about the initiative, as we did this morning, and as they are rolled out in the future.

BCBSA is committed to making sure people have timely access to safe and effective and affordable cutting edge prescription medicines when they need them. We share the FDA's concern about methods by which the agency's regulatory structure is being gamed to the detriment of consumers. Currently, there are significant barriers that hinder patients' timely access to generic and biosimilar medicines. We believe that promoting competition and consumer choice will make prescription medicines more affordable.

Specifically, the emerging biosimilar market in the U.S. provides great promise to further the goal of providing consumers with access to lower cost medicines. BCBSA supports a robust biosimilar market that ensures providers and patients have unbiased information available to them about the benefits of biosimilars. We recommend that the FDA and Congress address anticompetitive strategies and tactics aimed at delaying the availability of biosimilars, and that FDA ensures that policies for labeling and naming and

interchangeability provide the clarity and safety and avoid unnecessary regulatory hurdles.

With both the biosimilar market and the small molecule market, Congress enacted patent and exclusivity laws that create monopoly markets for new drugs, followed by the introduction of generic competitors. We have seen activity in the prescription drug market that has tipped the scales and upset this balance. BCBSA recommends the following steps to allow market forces to work more effectively and efficiently.

The first recommendation addresses the limited distribution systems and/or the use of REMS program to block generic manufacturers from accessing brand-name products. As we've heard today, some brand-name drug companies claim that providing adequate supplies of a drug to prospective drug manufacturers in the generic market would violate their REMS program. And other brand manufacturers use limited or restricted distribution systems for drugs, even for those drugs without a REMS, to the same effect. We encourage the FDA to recommend to Congress changes that will address these anticompetitive behaviors. BCBSA supports the

Fast Generics Act and the CREATES Act, which discourage companies from using restricted access programs to avoid generic competition.

Second, the success of a generic market is dependent on the ability to substitute generic products for brand products at the doctor's office and at the pharmacy. The practices of evergreening and product hopping are direct challenges to the generic market, and lead to increased spending on prescription drugs without any measurable improvements in quality or outcomes. Preventing such tactics will bring generic options and lower costs to consumers more quickly. We recommend that the FDA monitor activity that may be deemed anticompetitive, such as when an originator product is removed from the market and is replaced by a reformulated version. And also, to work with the appropriate federal agencies if antitrust laws have been violated.

Our last recommendation to rebalance the Hatch-Waxman scales is for legislation to ban pay for delay agreements, where brand drug manufacturers pay a generic drug manufacturer, or make other financial

arrangements, to not bring lower cost alternatives to the market. The FTC estimates that these anticompetitive arrangements cost taxpayers and consumers up to $3.5 billion in higher drug costs. Given the FDA's interest in seeing generic products reach consumers in a timely manner, we encourage the agency to assist the FTC in its review of such cases, and advise Congress on legislative solution.

I have two final comments. The first is BCBSA's support of the FDA's efforts to reduce the generics backlog and expedite approval of generics. We are encouraged that the resources of GDUFA II, once approved, will assist the FDA in this herculean task.

And second, we request that the FDA examine a policy that would prioritize the review of brand-name applications where there is little or no competition, similar to the FDA policy that was announced for generics last month and was mentioned by Alex Brill this morning. The FDA drug application review process could be improved to prioritize branded products where there are no competitors in the therapeutic class. With the right solutions that increase competition,

choice and promote value, we can deliver affordable prescription drugs while protecting and supporting the essential innovations to deliver new treatments and cures to patients. Thank you for your time and consideration.

MS. DICKINSON: Thank you. I have a question about whether BCBSA or other entities have actually studied what we've been characterizing as product hopping -- that is, changes to formulations or other characteristics of drugs that have changed dosing regimens, et cetera, to determine whether they have, in fact, made a difference in patient compliance or clinical effect.

MR. EITING: So, reformulations that have intent -- with the intent to improve adherence? We haven't studied that to my knowledge. I know some reformulations are created with that intent, to increase adherence by reducing from three pills three times a day to one pill one time a day. We haven't examined that exactly, no.

MS. DICKINSON: Thank you.

DR. UHL: Could I just seek a little bit of

clarity to your very last recommendation, which was something around brand-name policies -- to prioritize those for which there is no competition with that class. What -- could you be a little more specific there? Are you talking about the indication for which there's no competition, or are you talking about the pharmaceutical class, molecule? I'm -- you know, it would help to better understand what it is you're driving at.

MR. EITING: Sure. Looking at the molecular level -- so, instances where you could have potentially two or three applications moving through the FDA at the same process, or same time, and where -- or, even a year down the road, where a -- granted, a priority review of a drug would bring that drug to market more quickly. So, especially in cases where you would have a first in class drug hit the market, and then you would have manufacturers catching up to try to get their market into the same molecular class.

DR. UHL: Okay. But, you wouldn't necessarily be driving towards indication. So, for example, there's a first in class that treats -- pick

something -- MS, for example. You would want to prioritize similar in class molecules.

MR. EITING: That's right. Yes.

DR. UHL: Okay.

MR. BANKOWITZ: Good morning. I'm Richard Bankowitz. I'm the Executive Vice President for Clinical Affairs at America's Health Insurance Plans, or AHIP. I have no slides, but we'll submit detailed comments to the docket.

America's Health Insurance Plans is the national association whose members provide coverage for healthcare and related services to millions of Americans every day. We're committed to market-based solutions and public/private partnerships that improve affordability, value, access and well-being for consumers. We appreciate this opportunity to comment on issues surrounding high costs of prescription drugs, and the need for market-based solutions. And we applaud the FDA for focusing on this critical issue.

Prescription drug prices are out of control. When drug companies are granted extraordinary protections through the patent system or market

exclusivity protections, they have a monopoly and can set any price they choose and raise prices at any time for any reason, as we have seen in the well-publicized example of the EpiPens. We recognize that manufacturers who take large risks in developing new therapies should be fairly rewarded. However, when monopoly power is abused, everyone overpays, from patients, businesses, taxpayers, hospitals, doctors and pharmacists.

A study recently published in the Annals of Internal Medicine highlights specific examples of generic drugs that were subject to dramatic price increases, including hydrocortisone acetate, lidocaine hydrochloride, which increased from 92 cents per application in 2008 to $42.27 per application in 2013. The study found that generic drugs with monopoly levels of competition were associated with price increases of 25 percent to 73.2 percent. By contrast, generic drugs with relatively high levels of competition were associated with price reductions of -34 percent to -28 percent.

Rising prescription drug costs impose a heavy

burden on all Americans. A recent AHIP study concluded that 22 cents of every premium dollar goes to pay for prescription drugs, outpacing the amount spent on physician services, inpatient hospital services, and outpatient hospital services.

I have several recommendations for reducing prescription drug prices. Our recommendations for effective market-based solutions include, number one, delivering real competition; number two, ensuring open and honest pricing; and, number three, delivering value to patients.

First, delivering real competition. Reducing rates of -- reducing rules, regulations and red tape. The FDA should be provided the necessary resources to clear the backlog of generic drug applications, particularly for classes of drugs with no or limited generic competition. We strongly support the FDA's efforts in this area.

Stopping REMS abuse and other tactics. We applaud the FDA's new focus on the abuse of risk evaluation mitigation strategies -- REMS -- and other restricted distribution systems which have effectively

allowed brand manufacturers to form artificial monopolies to halt the development of generic alternatives. Anticompetitive tactics such as pay for delay and product hopping should also be prohibited.

If we're serious about promoting competition, there are other important steps FDA should consider. For example, creating a robust biosimilars market. Some of the costliest and the most expensive and widely used biologics have been on the market for decades without biosimilar competition. In order for biosimilars to generate promised cost savings for consumers, FDA regulations must promote a robust market, ensure that providers and patients have unbiased information about the risks and benefits, and do not allow pharmaceutical manufacturers to delay the availability or limit access to biosimilars by taking advantage of regulatory loopholes, or exploiting the patent system.

Two, targeting orphan drug abuse. The Orphan Drug Act is being exploited. AHIP has data for 45 orphan drugs available from 2012 to 2014 which shows that almost half of the utilization of these drugs --

that's 44 percent -- was for indications that were not orphan indications. So, we must make sure that we support manufacturers who are developing drugs to treat rare diseases, and that this process is not being used as a gateway for premium pricing and blockbuster sales.

I'll conclude by saying that the FDA should also look at open and honest pricing, publishing the prices. As part of the FDA approval process, we believe manufacturers should be required to disclose information regarding the intended launch prices. Also, evaluating the effect of direct to consumer advertising. We strongly support FDA's focus on the impact of direct to consumer advertising, especially given that many companies spend nearly twice as much on sales and marketing as they do on R&D. We urge FDA to assess the impacts of the growth of direct to consumer advertising, particularly broadcast advertising, and evaluate the best approaches for conveying information to consumers.

We have some other recommendations on informing patients about the value and effectiveness of therapy, and also on looking at outcome-based formulary

programs, which we will include in our written remarks.

Thank you.

MR. FLANAGAN: Thank you.

MS. SCHLAIFER: Good morning. I'm Marissa Schlaifer, a pharmacist representing the Pharmaceutical Care Management Association, or PCMA. I appreciate the opportunity to appear at this public meeting to provide PCMA's suggestions on ways to better balance access and innovation under the Hatch-Waxman framework. PCMA is the national association representing America's pharmacy benefit managers, or PBMs. PBMs administer prescription drug plans for more than 266 million Americans.

Generic drugs are important options that allow greater access to healthcare for all Americans. Through innovative utilization management tools, such as lower cost-sharing generic incentive programs and the use of mail service pharmacies, PBMs are continuing to drive generic drug utilization rates. Increasing the utilization of generic drugs saves money for patients and plan sponsors, and allows greater access to healthcare for all Americans. PBMs rely on generic

competition to provide the most cost-effective medications for patients.

PCMA and our PBM member companies greatly appreciate Commissioner Gottlieb's and the FDA's efforts to clear the generic backlog, and to expedite consideration of ANDAs when there are fewer than three existing drugs. We agree that competition is best to facilitated when at least three competitor products are on the market. PCMA's recommendations focus on five specific policy improvements to increase competition in the drug market and bring down the cost of drugs. PCMA will expand on these topics in our written comments, to be submitted later this summer. Our recommendations include ending the use of risk evaluation and mitigation strategies, or REMS programs, to thwart competition; ending the use of anticompetitive pay for delay agreements; stopping anticompetitive product adjustments, or evergreening; using accelerated approval to generate needed competition; and changing biosimilar naming practices to better encourage competition.

So, first, reforming the use of REMS. As

you've already heard, manufacturers are misusing REMS programs to prevent generic competition. While many REMS programs restrict product distribution as a safety measure, brand drug manufacturers have begun using these required restrictions to deny access to samples for generic manufacturers, who need the samples to develop generic versions of brand products. Brand manufacturers have also begun extending this practice to drugs that are not under the REMS program. For example, several brand manufacturers sell drugs under tight controls through a limited number of pharmacies, which have been used to prevent generic competitors from acquiring samples to conduct bioequivalence tests required for generic drug approval. One generic drug manufacturer recently testified to Congress that it took three years to execute a sample sharing agreement for one drug limited by such restricted distribution system. Through last year, the FDA received more than 150 reports from generic manufacturers unable to access drug samples. The misuse of REMS delays timely filing and approval of ANDAs, keeping drug prices higher than they would otherwise be by preventing more cost-

effective generic alternatives. One recent study found brand drug manufacturers used REMS programs to thwart competition for $5.4 billion in sales on 40 drugs.

PCMA supports efforts to stop the anticompetitive use of REMS. The House of Representatives is currently considering legislation, the Fair Access for Safe and Timely Generics, or FAST Act, that would make it easier for generic manufacturers to obtain samples.

As an example of other ways to encourage brand manufacturers to use REMS programs properly, one would be to condition Medicare Part D coverage on any brand drug on its manufacturer's proper use of REMS. There is already a precedent in statute that brand manufacturers must agree to provide Medicare a 50 percent discount in the Part D coverage gap to have their drugs covered. Perhaps requiring an addition to the pledge on the proper use -- an additional pledge on the proper use of REMS programs would give brand manufacturers a strong incentive to stop anticompetitive behavior around REMS. We therefore encourage the FDA and HHS to examine all regulatory or

administrative authorities available to limit these kinds of abuses.

Second, eliminating pay for delay agreements. As identified in the public notice of this meeting, the drugs described in more than half of all FDA approved ANDAs are never marketed, marketed following a substantial delay, or marketed only intermittently. Brand-name pharmaceutical companies can delay generic competition by agreeing to pay a generic competitor to hold its competing product off the market for a certain period of time. These so-called pay for delay agreements have arisen as part of patent litigation settlement agreements between brand-name and generic pharmaceutical companies. These types of agreements are anticompetitive, and prohibiting them will lower drug costs. The Federal Trade Commission, or FTC, estimates these anticompetitive deals cost consumers and taxpayers $3.5 billion in higher drug costs every year. PCMA supports efforts to prohibit or significantly restrict such anticompetitve agreements. Numerous proposals have been put forward to do so, including Senate Bill 124, which would have authorized

the FTC to initiate proceedings against parties to any agreement resolving or settling a patent infringement claim in connection with the sale of the drug. In the last Congress, the Congressional Budget Office scored such a proposal as saving $2.9 billion over ten years.

Under FDA regulations, when first filers delay entering the market, other generic manufacturers cannot enter, which can make these first filer patent settlement deals particularly harmful to consumers. We encourage the FDA to consider current regulations to the furthest extent it can, to allow for increased competition wherever possible, especially on patent settlements.

Third, anticompetitive product adjustments, or evergreening. Drug manufacturers use tactics such as product hopping or evergreening, submitting applications to the FDA for approval of a "new product" that is essentially the same as the original product. Examples can include extended release formulations, combination therapies that combine two existing medications into one pill. These product lifestyle management tactics artificially extend drug exclusivity

periods and delay the take-up of lower cost generics. We ask the FDA to continue to work with the Federal Trade Commission, which has argued that such tactics may be anticompetitive and unlawful, and to continue to take actions when drug companies employ unlawful tactics, that delay widespread use of lower generic option, and, two, support plaintiffs who present legal challenges regarding such anticompetitive behaviors.

Fourth -- also, as previously mentioned, allow accelerated approval for brand drugs to generate needed competition. The FDA grants accelerated review to new drug applications that address unmet medical needs. We believe unmet medical needs should encompass lack of access when brand products are priced high and face no or little competition. If the price of a drug is so high that a patient who needs it cannot afford it, a concept some call financial toxicity, the patient's medical need is still unmet.

Economic data show that additional entrants into a therapeutic class result in lower costs when they generate head to head competition. For example, the second entrant into the breakthrough hepatitis C

therapies resulted in price concessions of nearly 50 percent from the original manufacturer. As costs fell, health plans offered the drugs to substantially greater populations of patients, thus meeting existing medical needs that had previously been unmet. We believe the FDA should further interpret the Food, Drug and Cosmetic Act in guidance to permit unmet medical need to include unaffordability.

Finally, changing biosimilars' naming and labeling practices to better encourage competition. PCMA recommends that the FDA reconsider its current guidance on biosimilars' naming and labeling. The FDA has adopted a guidance on biosimilar naming that requires the use of a nonmeaningful suffix attached to the nonproprietary name. This approach is different than that for small molecule drugs, where no such suffix is used. We believe this confuses patients and clinicians, and can promote the mistaken belief that substitutable products are not. Substitutable biosimilars should bear identical names and labels to their innovator analogs. FDA should revise its approach for biosimilars to be consistent with that for

small molecule generic drugs. Such a change is necessary to promote development of a robust biosimilars market.

Thank you for the opportunity to be here today in this public forum. PCMA looks forward to working with the agency and other stakeholders to address these important issues.

MR. FLANAGAN: Thank you.

MS. SCHLAIFER: Thanks.

MR. FLANAGAN: Same question that other panelists have asked other presenters. Often reformulation produces a significant therapeutic benefit. Other times it's pejoratively referred to as evergreening. Can you offer additional detail or thoughts?

MS. SCHLAIFER: I think as far as -- we don't have official policy on that, but just as a pharmacist, you know, as we've seen things go from tablets to capsules we've seen the addition of aspirin or an antacid to products. I think extended release and sustained release products are definitely an improvement in therapy, but when they happen close to

the end of a patent expiration the purpose of that change becomes a little more suspicious.

DR. UHL: Okay. So, can I just follow up Keith's question? How would you advise the agency to identify that, or find ways to mitigate that or, you know, something -- I mean, we understand the concern about product hopping or evergreening, whatever -- whatever term you want to use.

MS. SCHLAIFER: Right.

DR. UHL: What advice can you give us, aside from please don't let that happen, to -- in order to help us do our job?

MS. SCHLAIFER: Yeah. I think -- that's a great question, and I think as we go and submit our comments to the docket we can definitely provide some specific recommendations. I do think it's -- and it's obviously the challenge that you're trying to address with the question. Is there a substantial improvement in medical need to the patient? You know, definitely I think one where I personally would see a difference is when you're combining two medications that are both on the market -- one is available OTC, that's -- I think a

question will -- but, I think as far as what the association's input is, we can go back and submit details on that when we submit comments to the docket.

MS. McCASLIN: Good morning. My name is Tiffany McCaslin, and I'm a Senior Policy Analyst at the National Business Group on Health. Our organization represents 413 primarily large employers, including 73 of the Fortune 100, who voluntarily provide group and other employee benefits to over 55 million American employees, retirees and their families. We appreciate the opportunity to comment on the administration of the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, to ensure the appropriate balance between encouraging innovation in drug development and accelerating the availability of lower cost alternatives to innovator drugs.

We agree with the position that the life cycle of a pharmaceutical product as contemplated by the amendments includes a patent for a branded product followed by the expiry of said patent, followed by the entrance of one or multiple generic versions of that product to market, thereby increasing competition and

introducing downward pricing pressure on the branded pharmaceutical marketplace. We are very pleased that the agency has taken up this important issue, and within the context of the notice in the federal register our comments will focus on question number 1.

Current permissive patent and exclusivity period protocols may unduly delay market entry of lower cost alternatives to brand medications. After a generic or biosimilar is approved by the FDA, in many cases it may still take years for these less expensive medications to come to market, often due to litigation by the manufacturer of the original drug over outstanding legal questions about whether patent protection can be extended.

Employers and other members of the public have trouble understanding why this happens. Meaning, how can this claim of protection extend well beyond the original intent of the underlying patent. There can be multiple patents for one product covering different indications, delivery methods and/or combinations of the product. In fact, determining when a patent expires often requires specialized legal expertise.

One publication by CDER states that patent and exclusivity are the two most commonly searched terms on the FDA website, underscoring both the complexity and the value of these product protections to drug manufacturers as well as the level of interest from outside stakeholders. Beyond statutory extensions due to delays by the Patent and Trade Office or the FDA, the life of a drug's overall patent protection can be extended by applying for secondary patents through new formulations of the drug, new routes of administration, new indications or uses of the drug in combination with another drug. All of these lead to what we call patent estates.

Unfortunately, what we sometimes see is repeated and dubious use of the patent system to extend periods of market exclusivity, which adds to the growing unaffordability and unsustainability of pricing and spending in the prescription drug market. The costs of extended monopolies in the pharmaceutical market are more than just financial. They reduce patient access to needed medications and can serve to threaten further innovation. Therefore, policies that

extend patent protection terms or exclusivity periods should be revisited by policymakers and regulators. We have attached an addendum to our comments, which outlines specific patent abuses and other anticompetitive practice in more detail.

While these practices do not in effect extend original patents, they do create the patent estates I mentioned earlier, which increase the probability of litigation between brand and generic manufacturers. Additionally, building patent estates tends to run incongruence with the applications for additional market exclusivity from FDA.

We have four specific recommendations for policymakers, including eliminate or limit additive patent extensions and exclusivity periods that serve only to extend monopoly power, especially where there is limited or no additional company investment or patient value produced. Develop sound policy that would discourage patent abuses such as evergreening and product hopping. Eliminate pay for delay deals and/or implement penalty provisions for companies that engage in these types of arrangements, and finally reduce the

market exclusivity for biologics from 12 to 7 years.

Thank you for the opportunity to comment.

MR. FLANAGAN: 1 p.m. One hour lunch. Return at 1 p.m., please. Thank you.

(Off the record at 12:04 p.m.)

(On the record at 1:04 p.m.)

MR. FLANAGAN: As with the previous presentations, I'll announce the first speaker but not the subsequent speakers. So, please approach the podium when the slide that lists your name and affiliation appears on the screen. And after your remarks, please remain at the podium to allow the panel an opportunity for questions.

Mr. Davis?

MR. DAVIS: Great. Thank you, and good afternoon, everyone. On behalf of the Association for Accessible Medicines (AAM), and our members, it's a pleasure to be here today. And I want to start by thanking the FDA and Commissioner Gottlieb for convening today's discussion and for your commitment to maintaining a balance between encouraging innovation in drug development and accelerating the availability of

lower cost generic alternatives for America's patients.

We particularly appreciate the Commissioner's initiative and leadership in advancing his recently announced Drug Competition Action Plan that he spoke to this morning to address regulatory issues that are impeding competition. AAM is the nation's leading trade association for manufacturers and distributors of generic and biosimilar medications. Our core mission is to improve the lives of patients by advancing timely access to affordable generic and biosimilar therapies.

I want to take this opportunity at the beginning to say that we are optimistic -- and there's been discussion this morning about the possible soon reauthorization of the GDUFA program -- and I want to say that we are optimistic about the reauthorization of GDUFA, and I want to thank the FDA for being such a strong and constructive partner throughout the negotiations to get to an agreement that will truly benefit patients. As a result, we urge Congress to swiftly pass this legislation.

The Hatch-Waxman Amendments truly represent a model of successful bipartisan public policy. In over

its 30-plus year history, the amendments have produced a thriving marketplace in which generic drugs now make up 89 percent of all prescriptions filled in the U.S. market, but account for only 26 percent of total prescription drug costs to the U.S. healthcare system. This has important positive effects on public health, supports greater patient adherence, lower patient abandonment rates, and leads to longer healthier lives. In the request for comments, FDA described the balance between encouraging innovation and accelerating the availability of lower cost generic drugs as "critical to the public health." For the record, the Association for Accessible Medicines could not agree more.

There is abundant evidence that the innovation side of this balance has been flourishing. It's only July, and this year FDA has already approved more new molecular entities than it did in all of 2016. And that is terrific news, for everyone. Unfortunately, the competition side of the Hatch-Waxman balance is in jeopardy. This is due to a combination of factors, including a failure of policy to keep pace with changing pharmaceutical market dynamics and the abuse

of FDA laws, regulations and policies. While the innovation side of the Hatch-Waxman equilibrium has for decades seen an exponential series of incentives for drug development, things such as additional incentives and exclusivity provisions, additional tools and resources for drug development -- all of which are very important for patient health -- the reality is the access generic side has not received the attention that has been needed. When you combine that with the market realities of today, it reinforces why this hearing and the Commissioner's competition plan are so important. We are submitting more extensive comments to the docket. However, for today I want to focus on the following key points: first, the realities of today's generic drug marketplace; second, the need to prevent gaming and abuse of FDA law, regulation and policies; third, the need to improve the overall efficiency of the generic drug review process; and, lastly, the importance of strong and effective leadership, both here at FDA and from other areas of government and industry, to achieve all of these goals.

Starting out, it is very important to

understand the current market dynamics that face the generic drug sector. In 2004, FDA published a study showing that a generic drug can cost as little as 20 percent of the branded drug, often referred to at that level as commoditized pricing, when eight or more competitors have entered the market. Those days are gone. More recent data suggests that this degree of price erosion, getting to commoditized pricing happens much sooner, often when there are as few as three to four generics in the class. And we heard some of that evidence this morning from several of the researchers.

The net effect of this is that it has produced great savings for patients, employers, insurers, the federal government and the states -- $253 billion in savings in calendar year 2016, alone. Our industry is very proud to be able to deliver these types of savings to the U.S. healthcare system. But -- and as you will hear from several of our members subsequent to me this afternoon -- our side of the pharmaceutical ecosystem faces significant and unique pressures that in many ways distinguish it from the monopolized branded sector. Generic companies face significant

consolidation in the wholesale and retail markets, where essentially three wholesalers, three GPOs and three to four retailers each are controlling between 80 and 90 percent of their respective markets.

We experience wide scale price deflation -- not inflation -- frequent supply fluctuations, higher ingredient costs, and increasing regulatory burdens, not to mention some of the barriers to entry that were discussed widely this morning, used to forestall competition. Each of these factors impacts the generic market on a daily basis, including decisions individual manufacturers have to make upon entry and exit decisions. And they are particular acute in low volume markets.

When you look at all the challenges I've just outlined you have an even better understanding of why the competition side of the Hatch-Waxman balance is in jeopardy. If you need more proof, then I would suggest to you for the remainder of this afternoon session look at the balance of who is participating in this session in the public hearing. I can assure you, based upon my own professional experience, that if the innovation

side of the Hatch-Waxman balance was under any degree of threat to the extent that the generics are, you would see much greater brand company presence here this afternoon.

The use of risk evaluation and mitigation systems, or REMS and REMS like programs, and other restricted distribution strategies not required by FDA for patient safety, is not a new phenomenon and has been discussed widely this morning. I would particularly note that Commissioner Gottlieb, in referencing comments today and testifying to Congress recently, has noted the approximately 150 complaints that were submitted to the agency in that regard. It is becoming increasingly clear, if not abundantly clear, that the refusal to provide samples has become primarily about one thing, and one thing only, and that is preventing competition. In 2012, the Senate passed legislation that would have curtailed these practices. But successful lobbying, at the end of the day, ultimately kept it from being enacted.

We encourage FDA to take swift action in waiving its requirement to implement a single shared

system, when the failure to reach agreement would delay the launch of an otherwise approvable generic competitor. FDA should establish clear, transparent and enforceable timelines for negotiations on a single shared system. Such deadlines, with the understanding that FDA will waive the shared system requirement in the absence of an agreement, will help remove the incentive to prolong the process unnecessarily. But, we also recognize that there is a limit to what FDA can do on its own.

As you have heard from other speakers today, we support the fact that Congress needs to take immediate action through the pending bills in the Senate and the House, the CREATES Act and the FAST Generics Act, which are bipartisan legislation -- not often seen today in healthcare -- in the House and the Senate to prevent the misuse of REMS and restricted distributing schemes to delay generic competition.

Failure to act in this space will be significant, and it will only encourage further anticompetitive practices to grow, if not addressed. A recent study, and you heard from Alex Brill this

morning, estimated that the potential market for products subject to REMS or restricted distribution was worth more than $20 billion. Abuse of the citizen petition process was also widely discussed this morning. So, in the interest of time I will not go into additional details on that front, other than to say that AAM associates itself with the remarks made by many this morning expressing their concerns on the potential misuse of citizen petitions.

In terms of other regulatory priorities, ensuring continuous and consistent transparency and communication between the FDA and the industry is essential to optimize the development, prefiling and review process for generic drugs. It is also important for FDA to address the bioequivalence guidance processes and practices to ensure that applications already under review are not held to shifting standards that may not have clinical relevance to safety and efficacy of a particular medicine.

We are very encouraged that the FDA is continuing its focus on improving the processes for approving generic versions of complex drugs in a timely

manner, another topic discussed earlier today. Many of today's generic products are scientifically and technically more complex, requiring FDA reviewers to possess more knowledge about new technologies and advances in the drug product manufacturing area. GDUFA II will aid and support this effort as we move forward.

And we respectfully encourage the FDA to promptly withdraw its proposed rule supplemental applications proposing labeling changes for approved drugs and biological products which, if enacted, would lead to provider and patient confusion and add costs unnecessarily to the system. FDA is not responsible for all of these issues that I have discussed today. It will require all of us, including payers, the FTC, CMS and other federal agencies, as well as Congress, to play an active role. Even the branded manufacturers in a recent report have publicly talked about in a public relations campaign the importance of incentivizing generic competition. It's time that we all work together to make that happen.

Thank you again for holding this hearing.

DR. UHL: Thanks, Chip.

MR. DAVIS: Sure.

DR. UHL: I apologize for arriving late for your presentation. I was dealing with another crisis. Could you elaborate, and maybe not here but in the docket, about AAM's thoughts on BE guidance and BE guidance development and practices? Because I think that would be relatively actionable --

MR. DAVIS: Sure.

DR. UHL: -- in the short frame -- I mean, the short term.

MR. DAVIS: Yes.

DR. UHL: Thanks.

MR. DAVIS: Dr. Uhl, we will --

DR. UHL: If you have ideas right now we're happy to hear, but --

MR. DAVIS: Yeah. No, I will -- we will make that as part of our docket submission. I would just say that I think the thing that we've heard, and many of our members will be coming up here, so they may have a perspective on this, is in part because of the regulatory review process and some of the time frames that have shortened under the tail end of GDUFA I and

we expect to shorten again under GDUFA II, that sometimes policy would be issued in that area where they were operating under a certain level of understanding and something shifted throughout the process. So, I think the acceleration of timelines will help that, and I think, quite frankly, the level of engagement between the agency and sponsors earlier in the process will also help alleviate that.

DR. UHL: And I think what would be helpful is some reflection on the -- there are changes in our understanding of the product, obviously, throughout the product lifecycle that impact our thinking on bioequivalent standards. And so, you know, given industry's experiences how -- you know, how to address that so that we are up to date scientifically and up to date in a regulatory basis on bioequivalence when we're ready to approve a generic.

MR. DAVIS: Will do.

DR. UHL: Did that make sense?

MR. DAVIS: Yes. It did.

DR. UHL: Thank you.

MS. SIPES: Thanks for your remarks. I had a

quick follow-up question for you. One of the topics that you mentioned had to do with factors affecting entry and exit decisions, and you mentioned a number of different factors, including consolidation in the wholesale and retail markets, supply issue, barriers to entry, and others. Could you comment a little bit further on entry and exit decisions with regard to any of those factors? But also, I'm interested in the extent to which you believe companies in the generic market look at the activities of their -- of other generics, and the plans and activities of their other generic competitors.

MR. DAVIS: Sure. Just briefly -- and again, this will be, I think, probably a theme that you may hear about from individual manufacturers -- the value proposition in many ways historically, as we all know on the generic side, has been to get to that level of commoditized pricing in the marketplace, whether it was eight to nine, ten competing products a decade ago, or now as soon as three or four -- one of the compounding factors that has impacted that is the consolidation in the buying community, particularly for generic

medications. So, if you have three or four major entities that have grown in size and scale through mergers and consolidation within their own sector of the supply chain.

It is harder, from simple economics, to see 10, 12, 14 different generic manufacturers all competing for the business of three or four large-scale wholesalers or retail pharmacies that are going to control 80 plus percent of their various distribution systems. So, what that ultimately leads to, and one of the concerns that we have, is that if you see additional consolidation -- I'm thinking one of the academic reports this morning they talked about having a small number of companies with very wide-scale portfolios, and then a large number of companies with very small portfolios -- what you've actually seen is an elimination in many ways of some midsized companies, that have either been acquired or ultimately divested into a couple of smaller companies. So, I think it's a marketplace reality that, I -- you know, we are looking at in terms of recognizing the importance of not just competition -- I think that's what you've always heard

from the generic sector.

We are focused on sustainable competition. How do you get companies that decide early on to file with the FDA, once they file, go to market and then once they're in the market, stay in the market? So, we're going to be -- we're looking at various ideas that -- some of which will have a market impact, some regulatory, some would require legislation that will focus on more creating a sustainable competitive environment moving forward.

Thanks.

MR. LEICHER: Good afternoon. I'm Bruce Leicher, Senior Vice President, General Counsel, Momenta Pharmaceuticals. Momenta is a biotechnology company engaged in the development of biosimilar and interchangeable biologics, as well as complex generics and novel products. We use innovation to develop new cures and affordable medicine for patients. We want to thank you for scheduling this meeting. We believe there are seven steps the FDA can take today to remove barriers to affordable medicine and promote price competition. Then, the competition will spur

innovation and new cures and achieve the balance sought under Hatch-Waxman and the Biosimilar Price Competition and Innovation Act.

First, we'd encourage the FDA to promptly hire the staff needed to implement the new user fee agreements with the available carry-over funds. New reforms introduced by GDUFA II and BsUFA II have important innovations. They enhance communication, target review resources, ensure timely meetings that can accelerate development, and use staff more efficiently. But hiring staff is key to their success.

Second, the FDA can immediately stop abuses associated with restricted access to reference product and REMS misuse. Today, many reference products are not available to develop affordable medicine. Some brand companies simply refuse to sell their product to generic and biosimilar manufacturers. The timely access to originator product was unrestricted for many years, and understood to be a legal obligation. This time-honored practice is now being thwarted to block development of competitive affordable medicine. And the FDA can fix this problem by issuing a policy

confirming that under Hatch-Waxman and the BPCIA it has always been, and is, a condition of originator approval that reference product be sold to generic and biosimilar companies promptly, on commercially reasonable terms, for testing under the regulatory supervision of the FDA.

In addition, FDA should work with CMS to implement a policy that makes CMS reimbursement contingent on compliance with that policy. These actions could be taken without legislation.

Third, the agency should continue to lead with innovative regulatory science. Advances in science made it possible to develop complex generics without clinical studies, and biosimilars with analytical science and targeted clinical studies. Employing more scientists with analytical expertise and facilitating a science driven flexible approach to review is critical to industry, to attract investment, accelerate development, enhance product quality and make medicine more affordable. Clear guidance that new ideas and innovation are acceptable is key. Rigid 20th century approaches must not slow development of affordable

medicine, when innovative 21st century science is available today.

Fourth, for interchangeable biologics, issue an explicit policy statement in the Purple Book that an interchangeable biologic may be substituted at the pharmacy without the intervention of a physician. Confirm to CMS that a determination of interchangeability means therapeutic equivalence to the reference product, just as FDA did in the Orange Book. CMS relies on this finding for generic drugs to provide favorable reimbursement and is awaiting guidance from the FDA. The finding is needed to unleash development of more affordable interchangeable biologics.

Fifth, adopt a policy that state substitution laws must not conflict with the substitution of interchangeable biologics authorized under the BPCIA. A patchwork of state substitution laws, some of which facilitate substitution and some of which might not, will deter investment in interchangeable biologics. An explicit policy will provide certainty by rendering conflicting laws unenforceable and eliminate the barrier.

Sixth, issue a rule completing implementation of the proper name policy for biologics, to make it nondiscriminatory. Today, only biosimilar receive suffixes. Originator products do not. This is very confusing to physicians and patients, and creates a barrier to biosimilar adoption by suggesting biosimilars are different. The naming policy must be fixed to apply equally to all biologics as intended.

Finally, allocate application review resources toward truly novel cures, generics and biosimilars. Reduce resources assigned to incremental life extension products. Routine formulation changes or convenience features of existing products lead to product hopping and do not warrant the same priority as new cures or affordable medicine. Patients deserve new cures, and patients deserve affordable medicine.

In addition, promptly deny citizen petitions that seek to delay or prevent generic biosimilars, as others spoke about earlier today. Thank you for the opportunity to present our views, and we look forward to supplementing them with our written comments.

MS. TOUFANIAN: Thank you, Bruce. Could you

expand on your observation that currently it's your perception that there are inappropriate rigid scientific requirements that are outdated?

MR. LEICHER: I don't believe there are inappropriately rigid restrictions. I believe that there would be an increase in the flexibility and enhancement by just having a positive statement that facilitated the use of new ideas and new techniques. It's natural for all of us to rely on the way we've historically done things to do something. And a positive statement from leadership that it's okay to think about new ideas I think would make a real difference.

MS. TOUFANIAN: Thank you.

MS. DICKINSON: Thanks for your presentation. So, I have a question, as a lawyer. Is it your view that FDA already has the authority to effectively preempt state substitution laws?

MR. LEICHER: I -- it is -- that is my view. M view is that Hatch-Waxman had nothing in the statute that said you could substitute a generic drug at the pharmacy, if you go -- if you study the statute. The

BPCIA specifically includes in the language of the statute that an interchangeable biologic may be substituted at the pharmacy without the intervention of a physician. That's express language. And I would think any law that's passed that conflicts with that language would be superseded under the supremacy clause.

MS. DICKINSON: On the biosimilars front --

MR. LEICHER: Yeah.

MS. DICKINSON: -- there isn't comparable language under the Hatch-Waxman.

MR. LEICHER: That's correct. And it's not needed under the Hatch-Waxman. I'm talking about interchangeable biologics.

MS. DICKINSON: Be interesting if you -- obviously, this is outside the scope of this particular meeting. But, to the extent that you have a full legal analysis, it would be interesting to hear.

MR. LEICHER: No. I'd be happy to. I know we've shared some of that with Maryll a couple of years ago, And I can include that with the comments.

DR. UHL: Could you elaborate a little bit

more on your comment about how resources are utilized under application review, and could you also provide some feedback about how reallocating resources also makes sure that we meet all the deliverables under the different UFAs?

MR. LEICHER: No. And I, and -- absolutely, and I think -- a comment was made earlier that I think might provide some -- a good suggestion, that -- as I listened to it, which was if you look at applications that involve convenience or incremental change that occurred during the end of patent life, it would be rational, I would think, for the FDA to conclude that there is a presumption that that's not -- that that's incremental. And then the applicant could perhaps have a burden of showing that there really is a benefit.

And if it's not -- if it truly is incremental, then I would think it should not get the same priority as something that's inventing a new cure for patients or that's delivering affordable medicine to patients. And there's got to be a way to get through the question that was asked earlier, on how to tease out what's incremental and what's really delivering value. And I

think the time at which it occurs actually is a pretty good place to start. If it's really not that innovative and it only occurs at the end of patent life, one would -- why didn't it happen sooner. And I think that's one way to look at it.

And you could pick a time frame in which you might pick that presumption tied to whether it would be handled and approved in sufficient time for a generics company to actually develop a generic to that successive version before patent life -- the original patent life expires.

DR. UHL: Can I just follow that up, then? With a -- are you proposing that the agency then modify its regulations for how we regulate prior approval supplements to NDAs? Because at this point in time, those types of assessments -- such as you said benefit is not written into the regulations. So, are you proposing that there's a regulation change?

MR. LEICHER: I'm not sure I'm proposing a specific solution. I'm raising an idea that I think would deserve conversation to find the -- a way to think about it. But the -- I think where I think

you'll find consensus is that there are a lot of resources that have been devoted, as was discussed earlier, of the agency to products which may or may not be delivering the same value to patients.

MR. FLANAGAN: Thanks, Bruce.

MR. LEICHER: Thank you.

MR. FLANAGAN: We're going to have staff try to turn up the mic a little bit over there. And presenters, remember to speak directly into the mic, please.

MR. BOYER: I've never been known not to be able to be heard. But, we'll go for it. Good afternoon, and thank you for having us all here today. My name is Andy Boyer. I am President and CEO of North America Generics, for Teva Pharmaceuticals. Teva Pharmaceuticals is a global company that delivers high quality patient-centric health care solutions used by approximately 200 million patients in 100 markets every day.

We are the world's largest generic medicines producer, with a portfolio of more than 1,800 molecules in a wide range of generic products in nearly every

therapeutic category. In the U.S. alone, Teva generic medicines are used to fill one out of every six prescriptions. In specialty medicines, Teva has the world leading innovative treatment for multiple sclerosis, as well as late-stage development programs for other disorders of the central nervous system, including movement disorders, migraine, pain, and neurodegenerative conditions, as well as a broad portfolio of respiratory products.

There is no doubt, as my colleagues have mentioned, that a balanced implementation of Hatch-Waxman is imperative. As a manufacturer of innovative and generic medicines, we recognize the importance of new treatments and ensuring access to existing therapies. Both are essential. We applaud the agency's focus on improving generic processes, eliminating the backlog of applications, removing unjustified barriers to competition, and speeding generic approvals. These are practical solutions to improve the existing regulatory framework.

Working hand in hand with the FDA on novel scientific issues and the logistics of reviewing

thousands of applications is no easy task. However, it is certainly one that is vital not only to our industry but to the patients that we serve.

In a relatively short period of time, the generic industry has undergone major changes. In 1997, there were 335 ANDAs submitted to the agency. This number has grown significantly over time, peaking at 1,473 submitted to the agency in 2014. In 2000, generic medicines represented 47 percent of the approximately 3 billion total prescriptions dispensed in the U.S. Today, they account of 89 percent of the over 3.9 billion prescriptions dispensed.

Our engagement with the agency has also changed. As we find ourselves at the conclusion of our first generic drug user fee agreement, we are eagerly awaiting the passage of legislation to solidify our second agreement. The agency and our industry representatives that work diligently to improve communications, address key issue areas and increase funding to fulfill our shared mission of getting safe and effective medicines to patients. We must continue to build upon our successes, improve the quality of our

interactions, and make changes that reflect the growth and trends in the marketplace.

Communications from the FDA inform the planning and launch preparations inside our companies. In this dynamic marketplace, greater transparency of when an ANDA is granted exclusivity or when exclusivity is forfeited would allow companies to make the necessary decisions to enter the marketplace on the earliest possible date. Currently, it is often unknown for months or even years whether or not a first filer has run afoul of a forfeiture event under the statute. And approval letters can be ambiguous at times. During this time, subsequent filers are unable to prepare for launch, delaying competition.

It is also unclear in the context of 505(b)(2) applications what the conditions of approval are for any given therapy. This also can create a great deal of uncertainty, as to whether exclusivity will block a similar 505(b)(2) product within the same therapeutic class. This uncertainty leads to costly litigation, and hinders the introduction of these competitive therapies into the market.

We also look to the FDA's Orange Book to inform many of our business decisions. Better Orange Book practices, such as real time listing of NDAs and exclusivity periods for brand medicines, and listing of the therapeutic equivalence ratings for (b)(2)s, concurrent with approval, will improve industry knowledge and market competition. Improving the regulatory process should include eliminating any undue burdens on industry. Regulation that is more disruptive than beneficial will only hinder progress.

We look forward to working with the FDA to identify opportunities to fulfill this policy goal, and identify areas where regulatory reduction makes sense. Take, for example, the requirement to provide paper labeling and inserts with our medicines. Modernizing labeling regulations to allow for e-labeling would reduce the cost of medicines and improve the speed and accuracy of information for patients. These paper labels are a waste of time and resources. More often than not, they are discarded by our customers and never viewed in their paper form by the intended audience -- physicians.

I am joined today by Gregg DeRosa, our Global VP of generic, clinical and product development, and Scott Tomsky, our Vice President of Regulatory for North America. Along with their teams, they work closely with the FDA and on a day-to-day basis will offer more real examples of the improvements that can be made to advance the development, review and approval of generic medicines.

Thank you for your time.

MR. DeROSA: Good afternoon. My name is Gregg DeRosa, and I'm the Vice President of Global Generic R&D -- Clinical R&D. I represent Teva Pharmaceuticals. And today, there are a couple of items I'd like to discuss. First, I'd like to discuss recent changes to both general and product specific guidances. And two, a little bit about abuse deterrent opioids.

As science advances and new medicines and formulations enter the market, FDA must face the challenge of establishing sameness and bioequivalence for complex generic products. These are policy decisions that must be made and clearly communicated to

generic applicant sponsors to support our submissions. Changing requirements of both general and product specific guidances after the agency has received an ANDA for review is a significant challenge.

This has resulted in significant delays in approvals of generic products, requiring generic manufacturers to repeat formerly accepted tests as well as conduct additional tests. For example, the issuance of the draft guidance on assessing adhesion with transdermal delivery systems and topical patches for ANDAs, which was issued in 2016, has drastically changed the dynamic of measuring transdermal adhesion. All previously submitted ANDAs that utilize the criteria in the previous guidance must now meet very different and more stringent criteria. This clearly has and will continue to delay many products that were tested under the old criteria. Changes to product specific guidances, specifically for certain immediate release locally acting products, have completely redefined the submission requirements, and will inevitably delay generic entry. We can appreciate and support such changes when the changes are made to

enhance the safety of a product. However, such changes should be the exception, not the norm, and should not hold up products that have been under agency review.

The other topic I'd like to highlight here today is the need for definitive criteria for the approval of generic AD opioids. Teva is committed to ensuring the highest standard of safety and quality to develop generic abuse deterrent pain therapies. We believe the FDA should require all opioids, short acting and extended release, to have abuse deterrent properties and require generic versions to have abuse deterrent properties that are no less abuse deterrent but not necessarily identical to the brand. We believe that for a generic ADF to be considered AB to a branded ADF product, the generic must meet the traditional standard of bioequivalence, qualifying for the same abuse deterrent labeling, possess the same abuse deterrent characteristics, such as physical/chemical barrier, agonist/antagonist combination, and have no less of an abuse deterrent effect than that of the brand, as determined by the FDA.

Teva recognizes that there are several

variations of ADF products and technologies, and with these variations comes different testing requirements. With that said, we believe the closer the generic formulation is to that of the brand, the nature and grade of excipients, manufacturing process of the generic product to that of the branded product, the more heavily weighted the FDA's recommendations may be toward in vitro testing only. Conversely, the greater the degree or significance of difference between the branded and generic products, with regard to ADF technology, the more likely that additional in vitro, pharmacokinetic and perhaps human abuse liability studies may be warranted. Since the public meetings on this topic in 2014 and 2016, the FDA has approved ten branded ADF opioids. However, to date, there are still no generic ADF approved opioids available to the American public. This poses serious issues, including lack of access to needed affordable medicines for patients with pain. Generic manufacturers can help provide a solution to the opioid problem in the U.S., but need the FDA to provide the regulatory pathway for approval of a generic ADF.

Industry has made several attempts to obtain product specific bioequivalence guidance from the agency, as this guidance is necessary for the generic manufacturer to have a clear understanding of the testing required to make an approvable generic ADF. Teva urges the FDA to provide product specific guidance for the ten currently approved ADF opioids, and follow suit in an expeditious manner as new ADF products come to the market. This will help ensure a level playing field and allow the generic industry to help mitigate the risk of misuse and abuse while providing affordable pain options for our patients.

The generic industry can also help provide a solution to the innovator's problems with the FDA requirements of demonstrating post-market effectiveness in terms of ADF effectiveness. To date, the FDA has not awarded any of the ten branded products with post-marketing effectiveness claims, category IV, as drug utilization has been too low to conduct satisfactory epidemiological studies. Further to this, Blue Cross Blue Shield has indicated they will not reimburse for ADFs until the FDA awards innovators with that category

IV claim.

This clearly poses a serious conundrum. Once generic ADF medicines become available, drug utilization will likely increase, thereby increasing the denominator needed to better assess the post-marketing effect of ADF medicines, medicines for the FDA and for the payer community. Teva welcomes the opportunity to discuss these important issues with the FDA, and help the FDA further the development of generic guidance for generic ADF products.

Thank you.

DR. UHL: So, I'm curious if you could potentially expand a bit more about the bioequivalence. You know, as a new drug is approved, an NDA is approved, there are frequently some post-marketing requirements for that particular product. So, for example, food effect studies, drug/drug combination, things of that sort that help us better understand the performance of that drug product. So, how would you, Teva, or you, the generic industry, advise us on how we can best deal with evolving information and knowledge about a product so that when we -- when a generic comes

in or a generic is being reviewed or the generic is approved that it meets that level of knowledge and understanding of the product?

MR. DeROSA: Well, I think to your point -- I mean, perhaps when a product is submitted it should be viewed in the light of the guidance that it was submitted under. Once that guidance changes, I think a post-marketing commitment makes a lot of sense. But, not delaying approval.

DR. UHL: So, I actually am referring to post-marketing commitments per the NDA.

MR. DeROSA: Okay.

DR. UHL: So, while those are being reviewed a lot -- that may happen concurrently with ANDAs in house. So, how are we supposed to apply the, you know, standards of -- understanding of the knowledge of a valid product.

MR. DeROSA: Specifically, what are you referring to? Are you referring to my comments about overall bioequivalence, or more about the generic ADFs?

DR. UHL: Not about generic ADFs. I'm talking more generally about -- you talked about BE

requirements and BE guidance. And so, I'm just trying to elicit more feedback about how do we handle the evolution of product knowledge while we're making regulatory decisions.

MR. DeROSA: Well, I think specifically when I think about -- let's use the transdermal products, for an example. I realize that you -- there's been some knowledge gained over the years on how to assess certain aspects of a formulation. But, when we are actually submitting those products, we're utilizing the guidance that you've given us as the time. Right. And so, we are designing our entire bioequivalence program based on that guidance.

So, we've submitted it. It sits with the agency for a year or two. And then all of a sudden there's a new guidance, and that guidance changes the paradigm completely. That puts us at a significant disadvantage, and I think perhaps there is some post-marketing commitment that the generics could make to meet these guidances as our scientific knowledge evolves. But it's very difficult for us to have designed an entire program based on a guidance that now

no longer really is enforced. And we have no control.

MR. FLANAGAN: Thank you.

MR. DeROSA: Thank you.

MR. TOMSKY: Good afternoon. My name is Scott Tomsky, and I am Vice President for Regulatory Affairs for Teva Pharmaceuticals North America Generics. My colleagues have raised several important topics today. I would like to talk in more detail about some of the process and approval challenges we face. I thank FDA for this opportunity to have these important discussions, and look forward to continuing to work with them to speed safe and effective generic medicines to patients. Commissioner Gottlieb's commitment to the approval of complex generic drugs builds upon the agreement with FDA during user fee negotiations, to work closely with ANDA sponsors and address outstanding policy and scientific issues that have caused delays. Further transparency and communication between industry and FDA will foster higher quality, right first time submissions that can be approved in fewer review cycles, increasing access to more affordable generic medicines. And we are

encouraged by the comments by Commissioner Gottlieb earlier today, about the impending MAPP as well as draft guidance to be issued by the end of this year.

One of the most important elements of the GDUFA II agreement is the bridging of GDUFA I and pre-GDUFA I files, and their inclusion in the GDUFA II metrics, guaranteeing goal dates for every file after October 1st of this year. Many existing applications have been under review for years, and I urge the agency to increase communication and transparency for these applications so FDA can take action in the form of an approval, rather than a CRL on these files in the coming months. It is these files which present one of the greatest challenges for our industry. Over the years, FDA continues to change the goalposts, and what may have been acceptable in the past to approve ANDAs is no longer the standard for many applications that were submitted years ago, Approved products are often not required to meet these revised requirements, while unapproved applications which met the requirements at the time of submission and matched those applications that have been approved are now penalized and held to

these new standards. These pending ANDAs, as a result, go through multiple review cycles, often requiring new batches to be manufactured, new studies to be conducted. These applications are taking away from resources from both FDA as well as industry, leading to less access and competition in the market, and therefore should only be held to new standards when it is absolutely necessary for safety reasons.

When guidance has changed for safety and efficacy reasons and a product approved as an ANDA is no longer considered equivalent to its reference product, and loses its AB rating, FDA must take swift action to have these products withdrawn. Allowing these products to remain on the market and substituted undermine the confidence of generic medicines.

Another key process and approval challenge we face is gaining approval of more complex medicines. There is currently a lack of cooperation and communication between the centers at the FDA. We are experiencing delays, for example, with combination products. Many of these products were submitted prior to enactment of GDUFA, and therefore currently do not

have goal dates. Rather, they have target action dates. And while some of these products may be a priority for CDER, they are not necessarily a priority for CDRH. We've experienced significant delays for such combinations products which require a consult from CDRH.

My colleague Gregg touched upon abuse deterrent opioid products, and for these medicines and others that have potentially serious associated risks, REMS are needed. To reduce the overall burden on the healthcare system, industry working groups are formed for multiple manufacturers to agree on a shared REMS strategy. In instances where this -- there is difficulty in coming to an agreement with the working group, FDA has to intervene more quickly. Lack of agreement to shared REMS should not result in the delay of generics to the market. I also echo the concerns raised here today by others that REMS restricted access programs should not be used to prevent generic manufacturers from obtaining samples for bioequivalence testing. This is clearly not the intention of these programs.

Finally, for some products that aren't suitable for submission under the ANDA pathway, organizations can achieve the approval of a therapeutically equivalent medicine through the 505(b)(2) process. In these instances, it's imperative that the equivalence rating be assigned at the time of approval of these applications, rather than the current process in delaying the listing in the Orange Book of the designation until a committee can meet to assess the therapeutic equivalence rating appropriateness. This prevents substitution, limits competition and increases the cost to the healthcare system. Take, for example, the injectable product azacitidine. Teva submitted a 505(b)(2) application that was approved in April of 2016. However, the therapeutic equivalence rating was not published in the Orange Book until April of 2017, one year later.

Thank you for your time today. Teva will be submitting written comments to discuss all these points in more detail, as well as points on the proposals to improve FDA's decision-making and communication practices, consistency of approval standards over time,

ending the maintenance of withdrawn applications, faster approval of complex products, reducing regulation and proposed regulations that present undue burden on manufacturers. Thank you.

MS. TOUFANIAN: Thank you, Scott. One of the things that -- I won't ask you to do a regulatory analysis on the spot, but I would request of you and your colleague who spoke previously with regards to your request about the appropriate standard to apply to an ANDA on submission when the bioequivalence or other recommendations for approval change -- I would request part of that analysis be in the context of the regulatory and statutory requirements. For example, our bioequivalence regulations require we use the most accurate, sensitive and reproducible method in evaluating bioequivalence. So, as part of your analysis I invite you to address the regs themselves, in that regard.

MR. TOMSKY: Thank you.

MR. FLANAGAN: Scott, Gregg, Andrew, thank you for this specificity.

MR. TOMSKY: Thank you.

MR. DUCKER: Good afternoon. My name is John Ducker. I'm the President and Chief Executive Officer of Fresenius Kabi USA. Thank you for the opportunity to provide comments on the important subject of ensuring that Hatch-Waxman continues to provide sustainable competition for generic medicines in the United States. My point of view is informed by Fresenius Kabi being a global healthcare company with more than 30,000 employees around the world, specializing in lifesaving medicines and technologies for infusion, transfusion and clinical nutrition. In the U.S., we are a leading provider of generic sterile injectable medicines. Our portfolio consists of more than 400 injectable drugs administered predominantly in hospitals and other clinical settings. These include chemotherapeutics, analgesics, and anesthetics used in surgery and a wide range of anti-infective and critical care drugs. We manufacturer these products in three states -- Illinois, New York, and North Carolina -- as well as several plants outside the U.S., and we employ more than 2,750 people in the U.S. in manufacturing, R&D and distribution.

When the FDA announced this meeting, it asked for input from the public concerning how best to preserve the balance Congress intended with Hatch-Waxman. We agree with Commissioner Gottlieb that the balance between encouraging innovation in drug development and accelerating the availability of lower cost alternatives to innovator drugs needs to be preserved for the benefit of public health. Availability of lower cost medicines is important. Sustained availability of lower cost medicines is critically important.

We all know that the use of generic medicines reduces healthcare costs. We also know that many do not fully understand or appreciate how the generic marketplace works. Our hope is that today's meeting and the steps announced by the Commissioner will help policymakers gain a better understanding of how the generic marketplace works, to the benefit of patients. I would now like to address comments to some of the specific questions FDA posed prior to this meeting. Firstly, exclusivity periods. Generally, the 180-day exclusivity afforded to first Paragraph IV ANDA holder

has stimulated the process of bringing generics to market earlier than otherwise would be likely. There are, however, disincentives in the forfeiture provisions for late ANDA filers, following a first filers patent settlement, that allows the parking of exclusivity, which prevents second filers from attaining approval 180 days later, and this should be addressed to promote further competition in the marketplace.

Turning to innovator drug product labeling, as you know the Office of Generic Drugs practice requires ANDA labeling to be exactly the same as the reference listed drug at the time of approval. When changes are made to the reference listed drug's labeling during the final stages of ANDA approval, that approval can be delayed by several months while the ANDA labeling is updated. FDA should allow for post-approval commitments for the labeling changes rather than requiring the label to be updated prior to approval, unless there is a significant and immediate safety risk associated with the labeling revision. In our view, the FDA could -- should consider that a post-approval

commitment from the ANDA holder generally provides no more risk than the RLD itself, because inventory of the reference drug, carrying the old label, will persist in the marketplace for several months.

Additionally, there are still numerous citizen petitions filed by brand companies regarding protected indications. This is generally done when the generic approvals are imminent, and the request is made to FDA for so-called safety reasons to block the approval of ANDAs that don't include the innovator's protected language in the labeling. In most cases, this is clearly a delay tactic, and there are numerous examples of FDA's denial of these petitions. We believe FDA should address this abuse of the citizen petition process, either in guidance or regulation.

I would also like to comment on post approval changes to innovator drug products, such as reformulations. The practice of making minor formulation changes and then obtaining a patent is a common practice by the reference list drug holder to continue market exclusivity. At the time the FDA approves these formulation changes, FDA should also

make a public determination about the reason for the withdrawal of the previous formulation -- safety or efficacy. Requiring ANDA applicants to file citizen petitions for such a determination is not an effective of FDA or industry resources, and only serves to delay competition. These determinations are best made during the review of the formulation, and not several months or years later.

Dr. Woodcock talked about wanting to understand the reasons for lack of competition in some cases. So, let me turn to marketplace dynamics and incentives. The competition created by multiple generics entering a market has been demonstrated to cause prices to fall dramatically. However, less efficient manufacturers or those receiving an ANDA approval several months after generic market formation may decide not to launch or to withdraw their product from the marketplace because margins have turned negative. So, competition initially has a beneficial impact on prices, but when prices are driven too low in a commodity market, like generic medicines, competition falls away.

Remember that many generic drugs sell for a few cents per dose, and unlike branded medicines have very slim margins. As a point of reference, in 2016 Fresenius Kabi's average selling price across our entire portfolio was $5.09 per unit, about what some of us here paid for our Starbucks latte on the way in. Remember that we only market sterile injectable drugs for use in acute care settings -- not oral solids. A healthy sustainable generic marketplace requires pricing power to be in balance between buyers and sellers or manufacturers. This balance has been disturbed by the tremendous consolidation that has occurred amongst buyers, namely group purchasing organizations on the acute side of the healthcare system and retail pharmacy wholesaler alliances on the retail side. There are, in effect, three major buyers in both the retail and acute hospital markets, and each prefers to list only a single generic version of a particular drug. This increasingly means there is only room for three manufacturers in the market. This increases the risk of drug shortages, because the number of manufacturers of any one product may be

limited.

You may also be aware that generic drug manufacturers take a very modest share of the profit in the generic pharmaceutical supply chain. A recent study by the independent USC Schaeffer Center for Health Policy and Economics showed that for every $100 paid for a generic drug, manufacturing costs represent $18 and the generic manufacturer typically makes another $18 to offset their development and distribution costs. The remaining $64 goes to others in the supply chain, specifically pharmacies, wholesalers, insurers and pharmacy benefit managers. I would ask you to reflect on whether these downstream profits are appropriate in the context of the current concerns about drug pricing.

Good competition must also be fair competition, and that means FDA must take steps to ensure consistent compliance inspection standards are adopted across all facilities supplying the United States, whether here or overseas. I do not believe this is the case today.

And finally, FDA asked are there market niches

where the Hatch-Waxman Amendments' incentives to develop an ANDA are insufficient. For marketed unapproved products, there is no exclusivity awarded for bringing the product through the approval process. The only exclusivity is that which results by default for the time it takes a competitor to get an ANDA approved. These products being on the market for so many years rarely offer any new patent opportunities, so there is little reward for all of the financial and R&D resources expended in filing an ANDA and bringing it to approval. FDA should consider an exclusivity period equivalent to a new chemical entity.

So, thank you for the opportunity to speak on behalf of my company, on behalf of patients who benefit from access to affordable medicines. I believe that the generic pharmaceutical industry shares many of the same objectives with Commissioner Gottlieb and the agency, and as a board member of AAM I would welcome a more transparent and regular dialogue with FDA so we can get things done together. Thank you.

MS. DICKINSON: Hi. You made one assertion, and I wonder if it's backed up with any studies. And

that is the extent to which 180-day exclusivity is a motivator for companies to enter into the marketplace -- to provide an adequate incentive. Has AAM or are you aware of other studies that have been done to support that, that survey, the extent to which otherwise risky product development might be undertaken with the promise of exclusivity?

MR. DUCKER: Are you talking about the first filing Paragraph IV ANDAs?

MS. DICKINSON: Yes. 180 day -- the promise of 180 day.

MR. DUCKER: Yeah. Okay. It's how the industry works. It's the only way we make money. We don't make money unless we're first to market, and we take advantage of that initial steep price curve. When the market is commoditized, none of us are making much money. We wouldn't exist as companies if it were not for the 180-day exclusivity. We don't need to do a survey. I mean, we could have a show of hands here from every manufacturer --

MS. DICKINSON: I can imagine. I can imagine.

MR. DUCKER: -- in the room, I promise you you'll get the same answer.

MS. DICKINSON: And is there a -- have there been studies of the extent to which the first -- that exclusivity period is actually enjoyed, in the sense that the first -- a first ANDA holder actually launches its product and is able to be the sole or one of a limited number of marketers during that time period, as opposed to the exclusivity being forfeited or otherwise lost?

MR. DUCKER: I'm not aware of any studies in that particular situation. No.

MS. DICKINSON: Okay. Thank you.

DR. UHL: John, maybe I misheard you. You said something about there being three major buyers, and that they each only want one -- that's one generic of any particular. Can you explain --

MR. DUCKER: That's correct.

DR. UHL: -- the dynamics around that, and the -- or, maybe that's not you to explain and it's more --

MR. DUCKER: Oh, sure. Look, on the hospital

side where we operate most the -- most of the contracts -- most of the RFPs that GPO puts out are for sole awards. They're going to award their entire volume -- and remember the purchase power they wield, it -- you know, in the case of Visian it's nearly 50 percent of the entire hospital volume in the U.S., and they're going to award one supplier a sole award. So, you know, somebody wins. And there are two other GPOs that carry any significance in the United States. They're each making sole awards -- predominantly sole awards. Not exclusively, but predominantly sole awards.

If there are five generics and there are only three places at the table, two of you don't have anywhere to market your product at all. That's the dynamics. It's happening exactly the same way in the retail wholesale side. The retailers only want to stock one generic, and the brand. They don't want to have their shelf space, you know, taken up with five different generic versions of vancomycin. So, the same dynamic is happening.

You've had such enormous consolidation on the buy side, that's why you're getting consolidation on

the sell side. That's why manufacturers are having to consolidate, because there's no room at the table for so many manufacturers. It's just simple economics.

Thank you.

MS. McCLINTIC COATES: Good afternoon. My name is Marcie McClintic Coates, and I'm the Head of Global Policy at Mylan. With a 55-year history in working closely with FDA, Mylan appreciates the opportunity to provide comments to the agency's consideration today on this very important topic. Mylan has the -- one of the generic industry's broadest and most diverse portfolios, selling more than 635 products in the United States at an average sales price of 25 cents a dose across all major disease areas. Mylan provides more than 10 percent of all generics in the United States, and has more than 200 ANDAs pending with FDA, 45 of which are first generics.

Ensuring that the Hatch-Waxman system works to its full capacity to expedite access to low cost generics could not come at a more important time. Our nation's healthcare system is at an important inflection point, as we all know, given significant

recent changes for how medicines are paid. For example, patients have historically had two deductibles associated with their insurance coverage, one for medical services, such as hospital visits, and another for pharmaceuticals. Today, patients usually have only one consolidated deductible, and an increasing number of consumers are moving to higher deductible health plans. In fact, Kaiser Foundation estimates that at least 51 percent of covered workers must personally cover their out of pocket expenses on medicines until they reach their deductible of $1,000.

With even more patients expected to move to high deductible health plans in the near future, the availability of more affordable generic alternatives has never been more important. Based on the recent IMS report released in June, a generic prescription on average, on a price per prescription basis, is $30, compared to a brand product which is $667. About 90 percent of generic copays are under $20 for patients. So, those are tremendous savings. Every day earlier that a generic can come to market makes a clear difference to U.S. patients.

It is with this in mind that we share some general considerations to shape the thinking on this important topic, and look forward to supplementing the docket with additional examples. As the Supreme Court, has noted, it is the meaningfully different and special regulation of generics, under Hatch-Waxman, that has allowed the "generic drug market to expand, bringing more drugs more quickly and cheaply to the public." We believe two longstanding bedrock principles have historically contributed to the success of the generic program at FDA, and the agency's implementation of this critical law.

The first is FDA's commitment to carrying out the unique Hatch-Waxman Act of getting generic drugs into the hands of patients by approving generics on the earliest day that a legal barrier to approval no longer exists, and two, FDA's strong reliance on science to continuously improve and evolve the agency's thinking. This effort has resulted in generics representing almost 90 percent of prescriptions dispensed, but only 26 percent of the overall cost of prescribed medicine. In the last decade, generics have saved the U.S.

healthcare system more than $1.6 trillion. Mylan is proud to have provided more than $180 billion of savings in our generic portfolio over the last decade.

This success, though, of the generic program has led to shared challenges, as we know, for both FDA and industry, due to the number of generic drug applications submitted. To meet these challenges, FDA embarked on a significant effort to build a sustainable generic program under GDUFA, and it has been a significant effort, we might add. And just like any startup program, while there have been growing pains on both sides of the equation, I think the foundational work built is worth noting by the FDA staff.

With GDUFA I soon reaching its end, the agency now shifts its working with industry to reduce the number of redo cycles necessary to approval, and expand its focus on complex generics under GDUFA II. We applaud Dr. Gottlieb's interest in accelerating the availability and approval of complex generic products. As the recent IMS report found, complex and specialty products make up 32 percent of prescription drug spend today, but only represent 1 percent of the total

prescriptions written. That means the 10 percent of generic utilization that is not happening today is of extreme value to the U.S. marketplace and to patients who today do not have affordable generic alternatives. Continuing to find ways to provide more interactive iterative science-based exchange, both before and after submission of a complex generic, will help to encourage companies like Mylan who engages in the billions of dollars of research and development necessary to bring these products to market, providing greater predictability and earlier access to medicine.

Additionally, continuing to prioritize more timely generic approvals, including first generics, is equally critical, as the agency identifies ways to improve access. Recognizing the importance of the first generic approval, and the significant investment that is needed to develop a generic product, and engage in costly litigation needed to challenge questionable brand patents, Congress provided incentive in the form of 180-day exclusivity. FDA's continued prioritization of first generics, even as it works to further increase competition through additional approvals, is vital to

maintaining the Hatch-Waxman balance and incentivizing generic drug development in areas where consumers lack generic alternatives. And I would add that I concur with the statements made by John Ducker regarding the criticality of 180-day exclusivity. As 1984 has continued to evolve, that's incentive -- the one incentive that we do have. It's vital, especially as the expectations for continuous improvement in manufacturing and quality and supply chain, the ability during that 180 period is more important than ever.

The approval of just one generic can significantly drive down the prices of medicine at generic market formulation, and most often triggers, as we all have seen, the immediate entry of an authorized generic as well, upon that first generic approval. A robust Hatch-Waxman framework also requires that brand companies be prevented from manipulating the system to unduly extend their patent or exclusivity protections and otherwise delay the onset of generic competition. For example, as we've heard many times, the well-intentioned REMS requirements are constantly delaying the onset of generic competition. This is an abuse,

unfortunately, we've had more than a decade of experience in fighting against, and it's still not solved for. While we've all taken several steps to mitigate some of this, abuses continue to exist. These and other maneuvers by brand companies significantly delay and in some cases, foreclose consumer access to competition, through late-stage label changes, guidance comments that seek to impose unnecessary new requirements on generics are just a few examples we face. We look forward to working with FDA and AAM and others in industry to combat these efforts.

Lastly, as the agency considers ways to improve access to generics, additional opportunities exist for more efficient practices. Moving forward from -- to e-labeling from paper-based labeling is a great example of an effort that would reduce unnecessary regulatory and operational burden. With the increasing use of electronic health information systems, the availability of prescribing information in an electronic format can add further efficiencies to the healthcare system, in addition to reducing environmental costs and increasing patient safety

through the availability of real time updates to drug labeling.

In closing, these are just a few considerations and we look forward to supplementing the docket with additional detail regarding the questions raise in the federal register notice, as well as working with AAM on areas of common industry interest, including many of the topics raised in just this afternoon's discussion on guidance and label changes. We agree it would be helpful to determine whether such changes truly represent an imminent risk to public health, when evaluating whether a post-approval commitment can be made as changes are made later on, either to labels or guidances.

Thank you again for the opportunity to speak today, as well as comments to the docket. We are very encouraged by the opening by Dr. Gottlieb. Right out of the gate, some of the comments on the new MAPP as well -- both for industry and for FDA. I think that was a goal we asked for at the beginning of GDUFA I negotiations. I think the agency said that was a little premature. Looking back, I think it was. Now

is the right time. It's great to set that standard. That's a nice surprise, to hear that coming out. I think it's going to go a long way in getting us to the first cycle rate that we're wanting to get at, and it's overdue for generics.

Look forward to any questions you may have.

MS. SIPES: Thank you for your presentation. I had a quick question for you on your point about post-marketing commitments related to labeling changes.

MS. McCLINTIC COATES: Sure.

MS. SIPES: Could you say a little bit more about the range of labeling changes that you think could be addressed in that fashion?

MS. McCLINTIC COATES: Sure. I think that the -- you know, obviously, the statute came out and provided some relief for late stage label changes. But, as that is written it's pretty narrow in the very circumstance in which that can apply. And a lot of those abuses, I will say, have been curbed and we've been able to point to that statute for help. But whether it's label changes or guidance changes or the like, you know, it's part of that iterative sort of

science evaluation of whether something is a must have or a nice to have, in terms of right now versus post-approval. Are those changes that the brand is withdrawing product from the market to get into their marketplace, or allowing to have that current version on the marketplace and then supplementing with it, and so forth.

A lot of times especially toward the end this can add a lot of time, and days really matter in terms of access. Days can matter in the form of if it's a new formulation that the brand has switched to from the original formulation, and you're trying to get out there. Or it may be a difference of completely reprinting entire batches, which is at additional cost. The agency has in limited circumstances applied some discretion. We think there's just opportunity to revisit that, and possibly looking at that language as well to see if that could be expanded also. Fortunately, it's an area where I do think a lot of improvement has happened, and we should acknowledge that. But abuses do still exist.

Thank you.

MR. KRISHNAN: Hi. Good afternoon. My name is Kiran Krishnan. I'm the Senior Vice President for Global Regulatory Affairs at Apotex. I'm here to present Apotex's perspective on steps that can be taken to administer the Hatch-Waxman Act in a manner that better achieves Congress's goal of striking an appropriate balance between spurring innovation in the pharmaceutical marketplace and increasing patient access to quality, affordable generic medicines.

As successful as the Act has been, since its enactment, it has and continues to be routinely gamed in numerous ways to delay generic competition at great cost to the public. I would like to thank Commissioner Gottlieb, Dr. Woodcock, and Dr. Uhl and the OGD team for holding this hearing. Apotex acknowledges that the agency has taken significant steps to streamline the generic drug review process, and to the best of its ability to remove the roadblocks impeding generic drug approvals.

Apotex would like to highlight some additional steps the agency and Congress should take to further increase public access to generic drugs. Apotex will

provide very detailed comments to the dockets, but here, I am highlighting some of the essential elements.

First one is around the exclusivity structure. Apotex believes that the current 180-day exclusivity structure undermines more timely generic competition, by granting the award solely to the first applicant to file an NDA with the Paragraph IV certification. Under this system, subsequent filers have no incentive to continue patent fights that could lead to earlier competition if the subsequent filer were to knock out a patent that the first filer has left in place in a settlement. If the subsequent filer were to win, its competitor would be the beneficiary of that victory. The first filer would be permitted to launch upon the subsequent filer's victory. Despite being the party responsible for opening the market to generic competition, that subsequent filer would only be permitted to enter the market after the first filer ran its exclusivity. To promote earlier generic competition, the Hatch-Waxman exclusivity structure should be changed to grant exclusivity right to companies who win the patent challenges in addition to

ones who are first to submit the ANDA with the PIV certification.

To be sure, Apotex fully supports the right of generic companies to settle Hatch-Waxman patent challenges, because we don't believe the settlement in itself is a problem. We believe the fact that because somebody can settle in part the exclusivity, that's the problem. And that can be resolved if there can be amendments made to the Hatch-Waxman Act to allow a subsequent filer to fight out and win the patent litigation, and then enable that person to come to market.

The other aspect that I wanted to focus today is on product labeling and other product changes. The RLD holders slow down the process of ANDA approvals by introducing last-minute labeling changes and other formulation changes prior to ANDA approval that do not make the original or the most recent R&D less safe or effective. Example, addition of a sprinkle labeling to the product. The product itself has been approved for over six years. When the 30 month stay for the generic comes -- is -- it's coming along, the RLD holder tries

to get an approval for a sprinkle indication for that product. And then it actually creates a problem for the generic holder, because now they have to repeat a sprinkle study. This is just one of the examples, but there are many more examples where the RLD holders make labeling updates. The recent approvals of the generics for Abilify, generics for Gleevec, have -- are classic examples which are well-known to the agency where the brand holders game the system.

Apotex would also like to focus agency's attention on the patent listing process. RLD holders continue to manipulate the use codes, because they have not been standardized, even for products with similar uses. The FDA should review and enforce more standardized use codes that conform to the identified text in the product labeling and patent claims, and publish carve-out language where applicable.

In addition, Apotex would also like to request the agency or provide agency few comments to consider as it relates to streamlining the ANDA review process. A lot has been spoken about the bioequivalence guidance as a moving target. This in itself is a challenge when

-- for global companies like Apotex and many others that submit these applications to a lot of jurisdictions, including the FDA, doing the same study that was done for purpose of submission to the FDA. What we find is while the other regulators approve this application in the -- because when we kind of develop a dossier, it's a global dossier. It doesn't -- we don't develop a dossier that is specific for U.S. Now with the new stability requirement, we develop a global dossier. And the studies that are conducted are in many instances the same kind of studies that apply for multiple jurisdictions. But what happens is when the FDA changes its requirements, it is -- we have incur more time and, in some cases, like -- which was, again, highlighted earlier, the original NDA would have been submitted with one metabolite, or the parent compound. And then the agency comes back and asks us to monitor another metabolite. In those instances, we do not even have access to those plasma samples, so we have to -- or, we don't have -- we have to -- or, they probably wouldn't enough shelf life. So, you have to end up running another biostudy. It all adds up to the cost.

And also, I would like to highlight here on the drug shortage items, Apotex would like to appeal the agency on the drug shortage items to work with the sponsors to ensure that there is a process to rapidly review where there could be a phone technical discussion and not -- we have seen instances where drug shortage items are put into the same bucket as a standard ANDA in terms of its review requirements, and in terms of the screening requirements. So, Apotex would urge agency to consider a different set of screening requirements and review requirements for drug shortage items to ensure that there is rapid approval.

And lastly, Apotex will also request the agency to -- in the ANDA review process for the older applications, there -- that go through an endorsement phase, we've seen applications that sit in an endorsement phase for a long period of time. So, there has to be -- FDA should streamline this process by providing a maximum response time for endorsement phase, either it's for an approval or a CR letter, and should set time frames of not more than 30 days.

Lastly, I do concur with all the comments made

today on the REMS. So -- because a lot of comments have been made today, Apotex will submit its comment to the docket. Apotex does support the CREATES Act and the FAST Generics Act, as we believe that these offer bipartisan solution for addressing the problem. Thanks.

MR. FLANAGAN: Kiran, I'm sorry, my pen couldn't keep up with your presentation. Thank you for the specificity, and concision. You said -- on the first item, you said the settlement is not the problem.

MR. KRISHNAN: Yes.

MR. FLANAGAN: And then my notes say blank equals the problem. Can you expand on what the problem is?

MR. KRISHNAN: So, what I mean by that is the settlement in itself is not a problem. The fact that there is no incentive -- if I'm a subsequent filer, I have no incentive to go and fight a patent challenge. Because if I'm able to do it, if then it's -- then what happens is you as the agency can approve it. Right now, you cannot approve an ANDA application, because there is obviously -- or, even if you approve an ANDA

application that -- they can park their exclusivity. But you cannot approve a subsequent ANDA application because the exclusivity is parked.

So, all that Apotex is trying to request is to -- a process to amend possibly the Hatch-Waxman Act wherein the subsequent filer that is there will have the ability to fight the patent challenge and will be able to have a position possibly that is different than the first filer, and be able to get a favorable verdict from the court. As a result of which, it would force the -- right now there are provisions where it forces the first filer to launch within 70 days.

But the part of the problem is it -- you have to get a ruling from a federal circuit that cannot be appealed. So, we -- all we're saying is we don't have to go through that kind of process, but we want to go through a process where you -- being a subsequent filer, if you're able to get a favorable decision, if the agency can approve the subsequent filer then that creates competition. That actually -- in that case, settlement is not the problem.

MR. FLANAGAN: Got it.

DR. UHL: Kiran, I have a hand cramp because of how quickly you were talking. But --

MR. KRISHNAN: Yeah. I just --

DR. UHL: -- you did mention --

MR. KRISHNAN: -- had five minutes, so --

DR. UHL: -- towards the end drug shortage.

MR. KRISHNAN: Yes.

DR. UHL: And you said that we should consider different review or screening requirements. Can you expand upon that? What your thinking is?

MR. KRISHNAN: Yes.

DR. UHL: How many -- and if you have even deeper thoughts about that, to submit to the docket.

MR. KRISHNAN: Sure.

DR. UHL: I would love to hear what your thinking is.

MR. KRISHNAN: Sure. So, right now there is a standardized requirement for ANDA screening process. An applicant should come in with six months of stability at accelerated room temperature conditions. The DMF has had to have undergone a complete assessment, and there are all these standard

requirements. We appreciate that, and we follow that for every other ANDA.

But drug shortage is a different scenario. So, what we're saying is the agency should consider a mechanism by which you don't have to do a six-month stability at the time that we submit the application. Where -- because there were times when applicants who were submitting with three months of data. We understand, we've now moved on, we are in the six-month era.

But, then for drug shortage items all we're requesting is that the agency can consider accepting applications with three months of data, and as it relates to the DMF reviews or the screening of the DMFs, a commitment from the ANDA holder that -- and the DMF holder that we will resolve all inquiries during the review process. Because some of these applications, Dr. Uhl, you have to appreciate, are for items for which you can't find people who submit DMFs. So, some of these are newer players who are trying to submit DMFs. So, it's going to take them some time to get to the standards of documentation that is the

expectation of the agency.

So, all that we're trying to say is if there's a mechanism for these drug shortage items, where we have a more condensed screening process, and as far as the review process is concerned if there is an opportunity for more -- what -- discussions or post-approval commitments on some of the aspects, so you can enhance and move quickly to get the product to the market. But, again, as -- to your point, we do want to make sure that the products that are coming out are safe and effective and they are high quality products.

DR. UHL: So, by screening do you mean filing review --

MR. KRISHNAN: Yes.

DR. UHL: -- or are you meaning something different?

MR. KRISHNAN: Filing review.

DR. UHL: Okay. Thank you.

MR. FLANAGAN: Any other questions? Thanks, Kiran.

MR. KRISHNAN: Thank you.

MS. EDWARDS: Good afternoon. My name is

Candis Edwards, and I'm Senior VP of Regulatory Affairs at Amneal Pharmaceuticals. First of all, I want to thank Dr. Gottlieb and the FDA for convening the public hearing, so that we can examine the delicate balance between brand drug development and timely access to the -- by the public to more affordable generic medicines, which is embodied in the Hatch-Waxman Amendment.

As a bit of a background, Amneal Pharmaceuticals is a privately-owned U.S. company started about 15 years ago, by two brothers, Chintu and Chirag Patel, and today is one of the fastest growing global generic developers. We rank seventh -- I believe the seventh largest generic manufacturer in the U.S., and we have a diversified portfolio of over 100 products. We employ approximately 5,000 employees globally, and we're in the process of bringing about approximately 200 more products to the market within the next couple of years, where we'll be touching on all dosage forms in the generic arena.

So, what I'd like to do is present just a couple of concerns, possibly using some examples,

around the issues that we're here to discuss today. The first topic I'd like to talk about is the impact of changes to -- post-approval changes to formulations and how that could impact approvability of ANDAs, and I'll give an example here. So, we have -- and what we believe is that this is an area where they might be able to look at some administrative relief. So, most of my talk is going to be focused around where can we get some administrative relief, as opposed to statutory relief, which is probably easier to implement.

So, this example I have -- we have an injectable product. There's no generic equivalent. The original formulation was discontinued after FDA approved the newer formulation. And it was only minor changes to the formulation. We believed that the changes were some minor quantitative changes. There was no impact to safety or efficacy, and that was evidenced by the fact that the product still -- the original product continued to remain on the market. It was discontinued, but there's no recall or anything of that nature. So, that led us to believe it was just an issue where the brand, again, was making a decision to

move the product because there wasn't a generic approved.

In this instance, Amneal was very close to approval. And then there was also a citizen petition which was issued on the product, and it requested that the agency make a determination as to whether the product was withdrawn for reasons of safety or efficacy. So, to date the petition hasn't been resolved and what's happened is the combination of the petition and the formulation changes now creating some policy issues for the agency, and there's been no decision or delayed decision on the approvability of the product.

So, in order to rectify some of these unintentional product approval delays, we believe that the agency should have some procedures in place where we assure that you comply with the statutory requirements to address these blocking petitions in a more timely fashion. We also believe that it will be beneficial to the patients if there's some expedited review process in place to resolve those petitions that block generic competition when a product is single

source, and results in some unintended monopoly by the brand product.

Also, FDA may want to consider clear and transparent review process for the petitions, similar to that associated with some other user fee programs and include timelines for review and some mechanism for the petitioner to be updated to understand the impact of when that petition will be addressed.

Another area of concern for Amneal is a policy of revising bioequivalence requirements. There have been several speakers that have addressed that issue. And the concern is that these changes are made and the ANDA holders, we don't have any idea or any instructions because we've already fought -- we've conducted studies in the preexisting conditions. The changes occurred during midcycle review, and they can definitely impact the approvability of the ANDA if the FDA comes to a decision that because of the change in the guidance the study has to be repeated.

We understand that if the change impacts safety and efficacy, yes, this study needs to be repeated. That's a different issue. But there's some

changes -- simply a study design, we've had a recent one changed from normal healthy volunteers to patients, and probably that change might have been made for safety reasons, in conducting future studies. So, the study has already been conducted. It's safe, and it meets the requirements. So, you know, what -- there's a big question mark for us, are we going to end up with a complete response that says, well, the guidance changed so your study is no longer acceptable. So, that comes to the idea of transparency and understanding when these changes are going to impact our approvability, and not necessarily waiting until that ten-month goal date to say -- to get that letter, when in the meantime, if indeed it was determined it did affect approvability, we would have used that ten month period during the agency's review or whatever time that's left to repeat the study, and be prepared when that action was taken on the application.

So, what we're asking here is the agency implement an administrative policy that will allow review and approval of BE studies conducted under preexisting requirements when changes to the

requirements are made midcycle and the changes do not impact safety or efficacy of the product. Also, that you consider the impact of the products that are already on the market, not only how those changes impact the pending ANDAs but possibly there might need to be a need for those products that are already on the market to repeat some studies in some reasonable amount of time as well. So, that would be, then, something that we address there.

Another concern, first of all, regarding the REMS program has affected us significantly. We applaud Commissioner Gottlieb's recent emphasis related to REMS, and we understand the need for the REMS program for distribution of dangerous drugs. We believe the REMS serves a compelling public value. However, the companies frequently relying on REMS as lifecycle management strategy to block or delay generic market entry.

There are two concerns, one related to FDA's review of protocols in issuance of a letter of authorization to the brand to sell the samples to the generic company, and one related to the issuance of

waivers. So, with regard to -- we understand that there is no sample, there's not going to be a generic. So, the first area of brand abuse is in the delay or request for unreasonable requirement for the sale of samples to the generic -- in our experience, when a drug is covered by REMS, the brand often refuses to sell samples, either directly, or they request unreasonable contract terms when they're dictated through this letter to do so.

So, just as an example, starting in 2015 we submitted approximately seven requests for REMS protocol reviews, and the timelines were pretty long. First cycle review was 9 to 23 months. Second cycle review, because we had to make changes and resubmit, took about two to seven months. So, we're looking at -- we looked at an average of about 18 months for the agency just to review the protocols. And then to date, out of all of these products we've had two letters sent to brand companies and one which has resulted in actual product acquisition.

So, you can see that we think that the process needs to be addressed. We would ask that the agency

implement an administrative guideline on FDA response timelines for review of the protocols, under the current guidance, in perhaps three to six months, something that would be more timely. And then we also say that once the generic is developed, we are -- we have a problem with the impact of stalled negotiations with certain brand companies when we're working together toward a single REMS program.

So, another ask we have is that is it possible maybe to put some timelines, just as regards to the waiver. So, if we were to put a timeline to it, in effect say, okay, if you negotiated, let's say, for six months with the brand, you were not successful, then there would automatically be a waiver granted without further delay. And then we could move on in the process, have us some prescribed timeline there.

Another area that we ask the agency to consider an administrative policy is possibly adding a category or product classification in the Orange Book that might allow for the use of a similar RLD that is approved, let's say, under an EU jurisdiction, in a conduct of a BE study. So, more so the reference

standard, especially when there might be barrier to obtaining that product in the U.S. market. And we can provide evidence and confirmation that the two products are actually the same products, just marketed in different -- or, approved in different jurisdictions but manufactured as one product. So, for example, if the product is manufactured by a company and approved in the EU and the U.S. and the generic company is able to prove that, then the foreign product might be able to be eligible for use as a reference standard, just possibly for conducting the BE studies whereby we still would have our basis for approval, which is the statutory requirement for approval. So, we're talking about a common reference standard, possibly, by possibly recognizing EU approved products as a common recognition of EU and U.S. products.

So, I thank you for the opportunity to present our views. We do intend to provide further comments to the docket. And any questions, I'm available. Thank you.

MR. CALTRIDER: I had some slides. Are there slides -- there we go. I'm Steve Caltrider. I'm

Deputy General Patent Counsel at Eli Lilly and Company. Lilly is a 141-year-old innovator. Our company has been in the business of discovering, developing and manufacturing new medicines, particularly in diabetes and oncology. We've had recent success in diabetes and oncology. We've also done a tremendous amount of research in Alzheimer's, where we've been researching for 25 years and without yet developing a new medicine. But we continue our efforts.

None of what we and other innovators of new medicines accomplish would be possible without strong intellectual property protections. I will focus my remarks today on the first question raised in the FDA federal register notice. This involves the question, and the quote from Senator Hatch underscores its importance of how well the balance struck in 1984 is working for patients and for innovators and generic firms. In this law review article, Senator Hatch goes on to say that if the law and its administration can be improved, it should, and that is why we're here today.

Much has been written about Hatch-Waxman, and it's fair to say Justice Scalia noted that the statute

is not exactly easy to read. Federal District Judge Roger Titus made a more pointed comment than Justice Scalia.

Despite its complexities, the statute, most would agree, however, that Hatch-Waxman has been one of the most successful healthcare related laws ever enacted. The substantial savings generated by Hatch-Waxman, as identified by Dr. Woodcock, 1.46 trillion from 2005 to 2015, sometimes gets underappreciated in the debate over reforming the healthcare system.

I want to focus particularly on the segment of the market that makes generic copies possible in the first place -- pioneering drugs. Pioneering drugs are the innovation that treats the unmet medical needs -- the innovation that sustains the branded pharmaceutical industry and the innovation that the generic industry relies upon to sustain its business model when the patents expire. Simply stated, without an NDA there's not an ANDA. A healthcare system without innovation fails all stakeholders, most importantly patients waiting for cures. The next few slides are from a peer-reviewed paper coauthored by a subgroup of experts

convened by the Institute of Medicine. The purpose of the group was to identify the scientific and other barriers to making advances to address the many complex and debilitating nervous system related diseases, such as Alzheimer's.

The first observation that I would like to point out, that was made by the coauthors, is that the law is patent-centric. That is, useable patent life is the core incentive to justify the cost and the risk of the investment in CNS drug research. It is also noteworthy that since Hatch-Waxman was enacted in 1984, the U.S. as part of the obligations under the GATT Treaty has moved from a patent term of 17 years from issuance to 20 years from filing. This change in law is significant, as the patent clock starts running earlier. In disease states, such as neuroscience diseases, in this study, that have longer preclinical and clinical development cycles, the incentive contemplated by the 1984 act is significantly shorter than the 14 years originally conceived. It's critical to recognize that there is no causal link between patent ability and FDA approvability. Most patented

molecules fall by the wayside during the development process. To state the obvious, the patentability of a new drug doesn't contribute to whether the drug is sufficiently safe and effective to become a drug. It is an irrelevant consideration to the underlying science. But yet, it is too often the controlling consideration. An unpatented molecule could, as a matter of science, be both safe and effective in treating a disease, but it will never been developed as a drug. There are inadequate incentives to do so with the patent-centric focus of Hatch-Waxman.

One of the effects of the limitations or caps on Hatch-Waxman patent term restoration is that products which may require longer clinical trials, such as neuroscience trials, are not encouraged. Several questions can be raised about the caps. If 14 years is the period necessary to support innovation, the cost which has increased substantially since 1984, why cap restoration at five years? What is the benefit and justification for a five-year cap? Why should a day in clinical trials deserve only half the patent term restoration of a day in NDA review? Why doesn't the

time spent in animal and other preclinical studies deserve any patent term restoration?

In order to amplify the points, I've just made, I will refer to a 2013 study by three academic researchers from highly respected institutions -- Eric Budish from the University of Chicago, Ben Roin from the Harvard Law School, who is now joined by a third coauthor, Heidi Williams at MIT. The study is titled and raises important questions -- "Do fixed patent terms distort innovation?"

I encourage FDA and other stakeholders to review this study that analyzed over 46,000 cancer clinical trials that took place between 1973 and 2010. The authors examined empirical evidence and drew a number of conclusions on how the IP system affected the cancer clinical development pipeline. A central finding of the study is the observation that cancer R&D has been decidedly skewed toward end-stage cancers. The authors suggest this distortion is due in part to the rules of the patent system. In the opinion of the authors of this study, this is due to the fact that all things equal it takes less time to conduct chemical

research on these types of conditions than earlier stage cancers. In general, the longer the trials the shorter the effective post-patent life.

One of the points that the authors make is that the current system gives little incentive for development of preventative agents, such as potential prostate cancer vaccines, because the clinical trials would need to last longer than the life of the patent. The data on this graph raises questions about whether the current system is providing the right development pipeline in terms of public health.

One conclusion of this study is Hatch-Waxman is directionally correct in restoring patent term, but the suggestion to policymakers is that Hatch-Waxman does not go far enough. As you can see, the recommendation is that there ought to be reconsideration to more directly align the patent term with the date of FDA approval. Hatch-Waxman goes part of the way, but because of the five-year cap and other provisions it is patent-centric and skews R&D investment. I highly recommend all stakeholders to review the two publications that I just outlined. It

may be time to think outside the box and reexamine some of the very basic IP rules of Hatch-Waxman. This was certainly done in the case of biologics, where the 12-year data protection period was created in acts to make the law less patent-centric. There have been other proposals advanced by patient organizations on the Hill, and by such leaders as Senator Hatch, to create greater IP incentives that will drive more research investment toward unmet medical needs.

I've already discussed how the exclusivity periods set out in the Act have resulted in skewing research and development to be patent-centric. I'd like to briefly comment on the data period for new clinical indications. Due to developments in the law, induced infringement, the FDA practice of skinny labeling, and generic substitution, the exclusivity period, data package or patent exclusivity falls well short. In my opinion, the incentive contemplated by the Act for new clinical indications has really never been realized.

You really aren't able to discuss the delicate balance set out in the Act without considering broader

considerations. I want to turn briefly to this additional context. Under the current law, the litigation framework set out in Hatch-Waxman is not the end of the story. The America Invents Act introduced a new way to challenge patents at the Patent and Trademark Office. A patent can be fully litigated and upheld by the federal district court, and by the federal circuit court of appeals, through the Hatch-Waxman mechanism, and then the patent can be subject to further litigation before the patent trials and appeals board -- the PTAB, in a proceeding called inter partes review.

In 2016, nearly 70 percent invalidity rate was reported for patents reaching final decision before the PTAB, and only 15 percent of the patents have all claims that survived the proceeding. Imagine any endeavor with a 70 percent defect rate. This has been a major disruption to the balance in Hatch-Waxman. This is a complicated system, and people debate whether the invalidity rate should be measured by patent or by claim. There are also complex explanations for this dynamic. But I think it's fair to say the disruption

to innovators that rely on their investment of hundreds of millions of dollars, only to find these same patents are ruled invalid later by the same agency that issued the patents in the first place, such a defect weight will continue to only skew the system to be further patent-centric.

Thank you for the opportunity to discuss these issues with you today. I recognize that virtually all of what I've said is beyond the purview of the FDA to address through its existing regulatory authority. Your federal register notice announcement calls for discussion about the overall balance of Hatch-Waxman in today's environment. You cannot address the issue of balance through regulations without understanding the broader environment and the context. I hope these comments have provided some useful insight on how the IP environment colors the aspects of our R&D pipeline decisions. We have provided some suggestions about ways to improve the current incentives so that more of the thousands of currently unmet medical needs can be addressed. Thank you.

MR. KLEINHENZ: I also have slides -- thank

you. Good afternoon. Kenneth Kleinhenz, from Cytori Therapeutics. We are a very small pharma company in San Diego, and we do manufacture in the United States. I'd like to share with you my thoughts on a couple of very interesting comments that were made this morning. And one of those comments was that -- the question was why are there shortages in some of these drugs, and the second comment was that there are companies that are gaming the system to decrease competition. I'd like to give you a case study in that -- those exact concepts, with the liposomal doxorubicin product that we're trying to develop.

This all started in 2012, when there was a shortage of the doxuribicin liposomal form, and that the -- then the new facility was closed down and it resulted in a complete drug shortage. In this process, there was a citizen petition that had affirmed that the new reference standard was going to be the Sun Pharma product that's called lipodox. And in 2017 -- in April of 2017, the Orange Book changed and the change now listed the original NDA drug, Doxil, as the RLD, where it wasn't listed before. And keeping in mind that as a

small biopharma company, we need to know who the reference standard is so that we can do our bioequivalent studies. And that's very important to us.

When we look at the guidance document for ANDAs, we note that it's very clear that the bioequivalent studies are to be performed against the reference standard, and that the reference standard is now a Sun Pharma product -- we understand that and can follow that. And the guidance document even goes further to say that if the RLD is brought back to the market that the reference standard typically will remain as the BE -- bioequivalence comparator -- all makes sense to us. However, there is a product specific guidance document for liposomal doxorubicin, and this guidance document states that you can use the reference standard or the reference listed drug. And we find that very curious, although we do appreciate that flexibility. But, again, it does now seem to conflict with the ANDA guidance document that we cited previously.

The problem for us is that the Orange Book

reference was made in April 2017 to relist the RLD back to the original NDA product. However, there was no guidance put out regarding that. There was no indication for that coming through. So, it caught us all by surprise.

Also, it does create a conflict between the guidance document and the product specific guidance document. Now, this becomes a problem for us because what we would be looking for would be some specific guidance that comes out in the product specific guidance document that was reissued in April of 2017 also. And again, the guidance document was reissued but it always says the reference standard or the reference listed drug. And we would propose that there would be some specific documentation that would talk to the specific products in the product specific guidance document. It would really help to clarify the situation here, because it is highly unusual. And given the tumultuous product that was taken off the market, and now put back on the market -- again, there creates a significant amount of confusion in the industry for this specific product. Moreover, there is

another confusion where there are two products -- there's a Doxil product and a Caelyx product -- that are both manufactured by the same manufacturer, chemically equivalent in every way, and simply labeled differently for the European versus the U.S. markets.

And again, the question becomes why are there so few products on the market. When we are looking to make our decision on the bioequivalence, not only are we looking to do the reference standard or the reference listed drug now, we're also looking to determine whether or not there is a Doxil or is there a Caelyx. And again, the point here is that if the agency is flexible in accepting two completely different manufactured products, they should also be flexible in accepting the same product labeled differently for different markets. And this has been brought up multiple times today.

So, that is our request. We're just asking for clarity. We applaud the agency's efforts and simply ask for greater clarity on this very specific drug, especially given the fact that there is a product specific guidance document that really could use some

additional clarification.

Thank you so much.

MR. FLANAGAN: Thank you. Thanks.

MR. KLEINHENZ: Thank you.

MR. KORN: Thank you for holding this meeting, and inviting the views of the public. I'm David Korn, Vice President for IP and Law at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents leading innovative biopharmaceutical companies whose mission is to research and develop new and improved medicines for patients. PhRMA is here today to discuss the successes of Hatch-Waxman over the last three decades, and also to address some discrete issues that have arisen in implementing Hatch-Waxman.

Intellectual property, or IP, including both statutory exclusivity and patent protection, is the lifeblood of innovation, given the unique attributes of the biopharmaceutical R&D process, which is lengthy, costly and uncertain. It takes on average 10 to 15 years and costs $2.6 billion to develop a new medicine. PhRMA members alone invested in 2015 roughly $60

billion in researching and developing medicines. IP protection supports such continued future innovation in the long-term. PhRMA supports the important role of generic products for patients. The natural evolution of medicines is that after an innovator undertakes the time-consuming and expensive development process and obtains approval, it enjoys an appropriate period of IP protections following which a generic version becomes available for patients. Indeed, this is the very cycle that the Drug Price Competition and Patent Term Restoration Act, or Hatch-Waxman, attempted to encourage. Hatch-Waxman has fostered this competition through the timely entry of generics.

A few key facts. As FDA officials, have recognized, nearly 90 percent of all prescriptions are filled with generic products. And for brand medicines facing generic entry in 2013 and 2014, generics captured an average of 93 percent of the market by volume within a year of entry. Competitive pressure is expected to continue to fuel this dynamic in the years ahead.

The patent challenge procedure under Hatch-

Waxman is also robust, as multiple applicants typically challenge listed patents as soon as they are able. So, over 30 years after its enactment, Hatch-Waxman continues to strive for a balance between innovation and competition. However, PhRMA recognizes that there are certain areas where competition or incentives for innovation may be insufficient. The existing five-year data protection period does not alone sufficiently reward investment in small molecule drugs, particularly for the novel and complex drugs currently under development. Instead, the statute to provide more substantial incentives for development of new biologics with a longer data protection period that provides more certainty for innovators and more appropriately rewards innovation. When patents are also considered, patent challenges from generic manufacturers in the form of Paragraph IV filings have been filed more frequently and earlier in the brand-name drug lifecycle, with many as early as four years after launch. And the market exclusivity period before first generic entry for small molecules has declined over time, such that the brand medicines have faced generic competition at about 12

1/2 years after brand launch, even though the basic patent term is 20 years.

Combined with the uncertainties of the patent system, including the recent increasing usage of the IPR process at the Patent and Trademark Office, with some petitions filed even before the four-year mark, this could create challenges for innovative companies looking to develop new products. And efforts to further limit patent settlements would create additional challenges for companies.

On the other hand, review times for generic drug applications also have been an issue. PhRMA supports FDA's work to streamline and expedite the generic drug approval process, especially where there is no IP. In particular, we support FDA's steps to foster preparation of more high-quality generic applications to reduce the number of review cycles for these applications. Further, as FDA recognizes in its meeting notice, there are certain circumstances where existing incentives may be insufficient to spur generic development. PhRMA applauds FDA's recent actions to help address this issue, including by publishing a list

of off-patent, off-exclusivity drugs without approved generics and updating its internal procedures to provide for expedited review of certain generic applications. PhRMA believes there are additional steps FDA and Congress can take to address this issue, such as development of regulatory incentives for bringing such generic drugs to market.

PhRMA looks forward to working with FDA and, where appropriate, Congress to help address these issues, including swift passage of the user fee legislative package to foster increased competition.

I'll now address some specific questions raised in FDA's meeting notice. FDA's notice suggests that REMS with elements to assure safe use, or ETASU, "can prevent generic companies from obtaining drug products for bioequivalence testing" and may upset the intended balance of Hatch-Waxman. PhRMA believes that REMS are not upsetting the balance, that FDA has authority in this area and that legislation is not warranted.

First, FDA has used its REMS authority to approve a number of important innovative drugs with

serious safety risks, from cancer drugs to drugs for ultra-orphan populations that otherwise could not have been approved. Second, many drugs subject to REMS with ETASU have generic competitors or tentative approvals. Of the 42 REMS with ETASU programs, 10 are shared systems, meaning that generic versions have been approved. Thus, REMS with ETASU do not preclude generic competition. FDA has asked what additional actions it might take to promote generic company access to drug samples. PhRMA recognizes FDA's 2014 draft guidance, that sets forth a process for generic manufacturers to obtain letters from the agency stating that bioequivalence study protocols contain safety protections comparable to a REMS. However, this guidance has not been finalized, as noted earlier, and it leaves open important scientific regulatory and legal questions, which we identified in our February 2015 comments.

We urge FDA to address these key questions in a final guidance. This would give our members more confidence that when they provide samples to generic developers the samples will be handled and used safely,

and our members will not be subject to liability.

FDA's notice also asks how FDA should apply its statutory authority to waive the single shared systems REMS requirement to facilitate generic entry. PhRMA believes that FDA may more broadly exercise its waiver authority, based on the determination that the burdens outweigh its benefits.

FDA also asks how the citizen petition process has affected the balance struck in Hatch-Waxman. The citizen petition process serves as an important venue for raising critical scientific, policy and legal issues for FDA's consideration through a transparent constitutionally protected public process. Indeed, the statute requires that requests concerning abbreviated applications be submitted in citizen petitions under Section 505(q). Innovators have important contributions to make regarding these issues, due to their extensive knowledge and experience with the drugs in question.

Typically, 505(q) petitions are reviewed while FDA is also reviewing the related abbreviated application. Moreover, upon the deadline for

responding to the petition, FDA commonly issues an interim response indicating it has not yet ruled on the petition because of its complexity, or denying the petition without comment because the agency has not decided whether to approve the abbreviated application. And the statute already prohibits FDA from delaying approval of an abbreviated application due to a petition unless FDA determines "that a delay is necessary to protect the public health." FDA's own reports to Congress put 505(q) petitions in context, with only ten resulting in a delay of approval of an ANDA or 505(b)(2) application in eight years.

We also wanted to address FDA's question about how post-approval changes to innovator drug products affect the Hatch-Waxman balance. Post-approval changes, such as new dosage forms and routes of administration, are a critical part of pharmaceutical innovation, producing important treatment benefits for patients. R&D does not stop with initial FDA approval of a drug. A drug's safety and effectiveness are not determined solely by its active ingredient, and its therapeutic usefulness is not limited to the disease

for which it is studied initially. Post-approval changes can improve a drug's tolerability, effectiveness, adherence or convenience, and supports its approval for new diseases with unmet medical needs. Such continuous medical advances benefit patients and the public health, and should be incentivized by Hatch-Waxman.

Providing IP protection for such innovation does not negatively affect access to generic versions of the original product. Once the period of protection on the original product has ended, and provided there are no safety concerns, generic copies of that product may be approved. Healthcare providers and payers can then decide whether clinical benefits offered by improved branded products are more important than the cost savings available through use of less expensive generic versions of original products.

In conclusion, PhRMA looks forward to working with FDA on improvements to the biopharmaceutical ecosystem, including modernizing the drug discovery and development process and increasing competition for older medicines. We need a policy and regulatory

framework that fosters the continued innovation needed to address our most challenging diseases. Thank you.

MS. TOUFANIAN: Thank you for your comments. Could you describe in greater detail the concerns you have about the newly established IRP process, and how that undermines the balance that was originally created with the Hatch-Waxman Amendments?

MR. KORN: The -- you're referring to the process of the Patent Office?

MS. TOUFANIAN: Yes.

MR. KORN: Okay. It -- as was noted by the prior speaker, it creates another avenue for challenges that has people -- has companies defending challenges in multiple venues on different standards, and impacts just certainty as companies are looking -- trying to do planning. It adds an additional level of uncertainty.

DR. UHL: My pen moved a little too slowly.

MR. KORN: Sorry.

DR. UHL: When you were talking about post-approval changes, you said about the ability to improve tolerability, adherence -- I believe you had four specific examples that you used. So, my question is

should there be a requirement to demonstrate any or all four of those when the agency approves any postmarketing type changes to the innovator?

MR. KORN: I think that there is -- post-approval changes are just a natural evolution. And I don't think there is a reason -- although we would need to see any proposal -- I don't think there is a reason to have different standards for different approval changes, if they're otherwise warranted as being a safe and effective product going forward.

DR. UHL: Okay.

MS. SIPES: Thanks for your comments. Earlier in the day, there were some proposals made that the letters issued under the guidance you referred to be made public. What do you think of that proposal?

MR. KORN: That's something that we would need to consider. As I mentioned, we had a number of comments on the guidance as a whole. But we'll consider that proposal.

DR. STEIN: You mentioned that even though there is challenges in approvals with the REMS process that ultimately that hasn't led to substantial delays,

from the report you mentioned. Yet it clearly, from what we've heard earlier, has been a substantial burden. Can you just comment on how you would balance that? Clearly, there is the -- the efforts are substantial to try to overcome and to get to an approved REMS. How would you balance that?

MR. KORN: Well, I think we were looking at two ways of looking at it. And one is through the process with the letter. And then we can look at the factors, but I think the statute talks about in the -- for the single shared system has a number of factors that FDA could weigh in looking forward and trying to figure out what the right balance is. We don't have a proposal on that. We could think through that as well. But, I think it does give FDA a menu of factors to review.

MR. MURPHY: Thank you for the opportunity for BIO to present some comments here today. My name is John Murphy. I'm Deputy General Counsel for Healthcare at BIO. And I will do my best not to just repeat things some of my colleagues said, and try and give you some perspectives that some of BIO's more

diverse membership has. At the outset, we appreciate FDA's willingness to hear these diverse viewpoints on the important topic. And the biopharmaceutical industry supports the goals of the Hatch-Waxman Amendments, and strives to ensure a robust, innovative and competitive biopharmaceutical marketplace in the United States. In fact, last year BIO's board adopted a policy directing the organization to ensure we promote policies across the organization that ensure both a competitive innovative market but also a competitive generics biopharmaceutical marketplace. So, it is something that we hold very important within the organization.

And to that end, we believe FDA has done an admirable job in advancing the goals of Hatch-Waxman to date. The evolution of PDUFA and the newer addition of GDUFA and now biosimilar user fee acts have created what we believe is a marketplace for innovative generic biopharmaceutical products that has expanded greatly, and I don't think I need to restate the statistics that have been shown around here, other than to say that it is continuing to get even larger with the approval

recently of the fifth biosimilar to come to the marketplace, and then the discussion earlier today of almost 50 products, or at least programs, under review. We also believe that FDA's recent efforts to publish the list of products with a noncompetitive market dynamic, and coupled with a commitment to expedite ANDA submissions of generic versions of these products, should go a long way to help relieve some of the concerns addressed in the federal register notice. And I would probably amend that to say that some of the initiatives announced by Commissioner Gottlieb this morning wrapped around those other two previously announced proposals ought to probably go a long way in facilitating some of that.

What we -- probably makes sense to do is turn to some of the more specific questions that I think will help inform our comments. Much has been said by others about the sort of REMS products and the ability to access samples. And, you know, there is sort of another side of the point that we would like to raise on that issue. We hear from many of our more small biotech members on this topic, sort of on the regular,

and it is not so much a proactive policy suggestion but rather some words of, I suppose, caution from some of these members that simply obtaining a letter from FDA assuring that a product's sale won't violate a REMS, while crucially important in the discussion, is not the only component that our members have to consider when looking at these sample requests.

There are questions of indemnity and liability that often arise in the discussions between manufacturers and sample-seeking entities, and also there are true concerns about supply in some instances, for biotech drugs that are in some instances not produced in a capacity that allows for a lot of overage outside of what is made to meet the needs for patients. And it doesn't necessarily mean that there would be no access, but it means that sometimes the timelines prescribed or demanded for access to those samples are difficult for companies to meet.

And there's also concerns that have been raised by some of our companies about the sort of almost in, what seems like, recent mostly legislative discussions unlimited supply of sample products that

might be required, because biotech -- sometimes biotech testing, even in the biosimilar space, can go on for a longer period of time. And we have heard concerns from members that, you know, there ought to be some discussion about how to appropriately couch or have some guidance on to how to negotiate those discussions.

We also want to raise the issue about incremental innovation. A lot has been said today about some of the other names that that product lifecycle takes on. But, oftentimes some of the most profound innovations take place in the studying of what would otherwise be an incremental innovation. You know, the organization -- and we have discussed ways to propose to the agency new policies around that issue, and if we are able to come to agreement we would be happy to submit that for the written record, for your consideration. But at a minimum, we wanted to raise, you know, the concept that not -- you know, thinking about incremental innovation in a one aspect scenario wherein it might only be a product change that -- you know, to the type of pill, but also there's a lot of incremental innovation that leads to profound changes

for a patient's experience, or for the patient's ability to access medicines.

And then finally, I think David said it earlier but we would also submit to the point that, you know, manufacturer oftentimes have some of the best and most up to date safety information about their own products. And their ability to openly convey that information to FDA via a citizen petition process is crucial. And many of them don't take that process lightly, and have serious discussions and considerations at issue when they -- prior to filing those things. And it's an important component in the product lifecycle for their products.

BIO will be submitting comments for the record that we will happily supplement with any questions any of you have, and hopefully come to some agreements on some proactive steps you can take. Thanks.

MR. FLANAGAN: 2:50. 2:50 -- 3:30. Okay. Ten-minute break. We'll be back at 3:30.

(Off the record at 3:17 p.m.)

(On the record at 3:34 p.m.)

MR. FLANAGAN: So, as with the previous

presentations, I'll announce the first speaker but not each of the subsequent presenters. So, please approach the podium when the slide that lists your name and affiliation appears on the screen. And after the last presenter, I'll make very brief closing remarks and then adjourn. Mr. Love.

MR. LOVE: Thank you very much. Let me figure out how this works. The first topic I wanted to talk about was transparency. Evidence is important -- important evidence, rather, is lacking in many areas, including evidence used to measure and evaluate the performance of current policies that influence investments in research and development and decisions on drug pricing.

The studies by Joe DiMasi and other industry consultants lack transparency about basic parameters, and are often used to confuse rather than inform policy debates. There is a need for more independent and granular data on R&D expenditures. There are proposals to require greater -- outlays on R&D outlays, prices, revenues and other aspects of pharmaceutical markets. The most important initiatives as regards R&D are those

that require companies to report the enrollment and costs of each clinical trial relating to the marketing approval of a drug, and the third-party funding, tax credits and other subsidies relevant to financing the development of the drug.

Investments in research and development involve risks and capital that are correlated to the timing and phase and stage of the development. The more granular the reporting is of the trial costs, including as it relates to specific trials, the year in the expenditure which incurred, and the amount and nature of the third-party subsidies, the more useful the information will be to policy makers and the public.

Investors are entitled to transparency of certain basic economic facts that are material to the price of a security. The public, on the other hand, is typically barred from the most basic information relevant to drug development costs, pricing, et cetera. There are currently many transparency initiatives, including, for example, the U.N. High-Level Panel on Access to Medicines recommendations, provisions in

Senate Bill 771 and HR 1776, and state legislative efforts, of which there are many.

The FDA should insist on standardized disclosures of trial costs, R&D subsidies, and revenues from products, broken down at least by country, in terms of the international revenues. Federal agencies that fund research, such as the Army, BARDA, CDC and the NIH, should report on the enrollment and cost of each trial they fund, subsidize or co-sponsor. This is a practice that the National Cancer Institute used to -- they used to publicize their per-patient cost per trials, and the amount that they spent on trials in the past. They don't do it now.

The licensing of federally-funded research should be more transparent, as regards the entities requesting exclusive licenses, all of the terms of the licenses, the R&D costs, the revenues and prices of products sold and the distributions of royalties.

There should be more robust authority in the United States for the non-voluntary licensing of patents, and better discretion on how to determine remuneration in those cases. Bayh-Dole rights in --

both the march-in rights and the royalty free rights could be used in some cases, but only apply to a small number of products. 28 U.S.C. 1498, the government use provisions and statutes, when the patent is used by or for the government, are broader, but there are risks that it involves, in terms of setting the remuneration and the compensation, which could be addressed.

The general rule should be that when there is an excessive price, a shortage or a blocking patent, the monopoly rather than the patent -- or, I'm sorry, the general rule should be that when there is an excessive price, a shortage or a blocking patent, the monopoly rather than the patient should be at risk.

I want to illustrate a couple of recent cases. Last week, the Armed Services Committee in the United States Senate published a report which had a mandate for the Department of Defense to exercise march-in rights and the royalty free rights in cases when the price of a drug in the United States, a vaccine or other medical technology is higher in the United States than the median price charged in the seven largest economies that have a per capita income of at least

half the per capita income in the United States.

In Germany, on July 11th, 2017, the German Federal Supreme Court announced that it affirmed the decision of the Federal Patent Court to issue a compulsory license allowing Merck to continue selling raltegravir in Germany. And I provided here a brief quotation. So, you have these two examples, very recently -- this month actually -- one in the U.S. Senate and one in Germany, on this issue.

We think that exceptions are needed for all regulatory exclusivities. The test data in NDAs, BLAs, orphan drug, pediatric and regulatory delay exclusivities should be subject to limitations and exceptions. Policies that require duplicative trials, which are necessary during the period of test data exclusivity, violate Paragraph 16 of the 2013 Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

In Europe, regimes of risk adjusted cost sharing exist to avoid unethical duplicative experiments involving animals, you know, except for humans. Like, if it's a rabbit or if it's a rat they

invoke these ethical principles. But, they don't do the same thing for humans. But, I think they should do it for humans.

Federally funded drugs like Spinraza, which are ridiculously expensive and also protected by regulatory barriers to entry, such as the orphan drug exclusivity, undermine the benefits of Bayh-Dole march-in rights as a remedy. In Europe, after an initial period of market exclusivity, you can waive the market exclusivity on the orphan drug provisions in Europe, if you can demonstrate it wasn't necessary or appropriate. When the United States faces shortages of drugs, such as in the case of Doxil and Fabrazyme, test data monopolies should not be a barrier to registering drugs that are needed, as was the case in the Fabrazyme case, and it was used in excuses not to use the march-in rights.

The FDA pediatric testing exception can and should be reformed. We've recently been estimating the cost of doing these trials. These are things that the FDA requests from a company. There's a large number of drugs where the cost of doing a trial per child exceeds

$1 million, in terms of the cost that's imposed on the public. And in those cases, I think you need to secure alternative financing. That's an FDA imposed exclusivity which is exercised only at the discretion of the FDA.

This is a slide on asthma inhalers. My son is an asthmatic. He complained to me about this problem last week. As you know, the FDA used to have an exception that allowed the older CFC inhalers to be used for asthmatics. There is an environmental issue with that technology.

But, most people that have looked at it have said that the actual impact on the environment -- I'm not even going through with my -- somebody else is doing the slides for me, because -- yeah, thank you. Because I obviously -- yeah, thank you, I mean, because I forgot to do any of the slides. I'm just looking at my own slides, and not for the whole group here. So, if you got me -- that's right. Just -- if you could just keep going, I -- help me out, because I'm doing badly on this. All right.

So, basically, very little impact on the

environment of prohibiting the older inhalers. So, if you have a product like Ventolin, which was put on the market a long, long time ago -- it now has 15 patents on the Orange Book, and it costs between $50 and $80. I think the FDA could revise -- revisit this policy to allow the less expensive ones to do.

I've only got about two and a half minutes left. I think you're going to enforce the time limit this time around. So, I'm going to just skip this, except to say that in the areas of personal importation and parallel trade there's a lot going on in Switzerland and Italy in this area right now, in terms of as a way of addressing what they think are excessive prices on Hep C drugs. And these are, I think, really interesting cases. We generally think in most cases you should think about parallel trade as a remedy where you regulate the parallel traders for safety, as they do in Europe extensively, and have for years. But you limit the parallel trade to the United States normally with countries that have at least 50 percent of the U.S. GDP.

This is my last slide. I think it's the most

important thing. I think governments have failed to regulate monopolies in the public interest, and this hearing is an example of that. The delinkage paradigm is rooted in the idea that the incentive that companies need to invest in research and development does not have to be packaged in the way of a market exclusivity or a monopoly. They need money, and they should be rewarded robustly for successful innovation efforts.

But if you move from the granted monopoly to money, you get to rationalize your incentive system in a hundred different ways, including describing -- the examples given by PhRMA in the paper they cited earlier, from Professor Williams and others. All these discussions about -- in the executive order, and the discussions about performance based pricing or indication based pricing or performance based prices are all much easier to implement if you delink the incentive to the inventor from the price of drug. As long as you have the drug price be the incentive, you set up a conflict between innovation and access, innovation and affordability. Everything you do that reduces the price of the drug will be seen as a threat

against innovation. If you haven't heard it before -- and I'm sure you have -- you're going to hear it every time anything comes up that's designed to protect consumers or roll back excessive prices.

The way forward on this is not to just give up on controlling high prices. It's to recognize that this thing is a fundamental policy incoherence, as this U.N. panel has stated. The progressive way forward, in terms of avoiding, like, radical shocks in the short-term is to strengthen the methods that provide incentives that are not tied to the price of the drug at the same time that you invoke measures that reduce the price of drugs.

I think I've run out of time. Thank you very much.

DR. UHL: Okay. Thank you. You mentioned during the transparency part here that the NCI used to publish the cost per patient. Do you happen to know when they stopped doing that, and why?

MR. LOVE: I'm not sure when they stopped doing it. I was involved in a series of hearings in the early nineties, where some of these issues about

drug development costs and government funded drugs were -- and I know at that time we -- in the early 2000, we used to look at those things. I know that the cost was below $10,000 a patient on oncology trials, for example, at that -- about 15 years ago, when they used to publish those statistics.

DR. UHL: Okay. And then you also mentioned, all the way at the end, about incentives not linked to the price of the drug. Do you have any suggestions about what those incentives might be?

MR. LOVE: Well, I think the incentives should be in the form of money. For example, right now you grant a monopoly for the pediatric studies. That's a way of financing the -- you can -- you have studies that cost, maybe, $30,000 a patient to do, for the studies, and you're effectively giving the person an incentive that's, in some cases, $2 or $3 million a patient. That's not very effective. But, if you -- in the antibiotics space, Senator Franken has proposed, along with 15 cosponsors on his legislation, that there be a $3 billion fund set up to reward successful innovators in the area of antibiotic drugs, because

they don’t want to tie the reward for developing antibiotic drugs to the volume of the use of the drugs, because that breeds more resistance. So, there's, you know, a special issue in antibiotics.

In HIV, Senator Sanders proposed that the government put up a $3 billion per year reward system to the development of new drugs in the HIV space, of which in the last 30 years you have approximately one novel chemical per year being put on the market, decade in and decade out. And that was only from the United States of America, and it wouldn't include the rewards that would be forthcoming from putting the drug on the market in Japan, Europe, developing countries outside the United States.

I think this kind of -- Senator Franken and others have proposed that the National Academies do a study of the feasibility of delinkage in the area of cancer, in the area of HIV, in the area of antibiotics or all drugs. The National Academies is quite keen to do this study. And it would be great if the FDA personnel would engage in the terms of reference of such a study.

MS. SIPES: I had a quick question for you. Your fourth slide, on non-voluntary licensing. You state that the rules on compulsory licensing should be amended to provide more robust authority. Can you say a little bit more about the kinds of amendments you think would make sense?

MR. LOVE: Yes. I think there is -- you could write an entirely new statute. There's two simple ways you could do it. If you were to take the Bayh-Dole march-in rights, for example, which is now limited to subject conventions, which are those conventions that involve funding by the NIH, the Army or some other federal agency, you could say for medical inventions that that march-in rights could be extended to any drug, vaccine or medical device that's regulated by the FDA. And then you would have a better standard which exists in the march-in ring for compensation than you do in the government use -- the government use statute is more like a taking approach, and the jurisprudence all over the map in terms of how these things turn out, in terms of the compensation.

It's not well-suited for pharmaceutical drugs.

And it was originally fashioned over disputes on patents on building roads and airplanes and things that are defense related. But, I think that the discussion about, in a non-voluntary setting as to what the compensation should be should be clarified and there should be sufficient discretion that the agency is willing to move forward.

In the Hepatitis C case, where the consequence of the high price was a small fraction of the patients receiving treatment when you could have treated a wider group of people, and when the VA ran out of the ability to provide the drug to their own -- to veterans, the Veterans Administration turned down a request to use this authority, because they were uncertain as to how much you'd have to compensate. And it -- in the VA's thinking, if the drug was selling at that time for a very high price and they had a lot of patients, they felt if they went ahead and used the government march-in rights -- I mean, the government use rights under 28 U.S.C. 1498, they wouldn't find out for years how much money they would owe for having made that decision. And that stopped them. And what they did is they

robbed another program for veterans. They took another appropriation for veterans that should have benefited veterans in a complete different way, and took the money out to make sure they could pay for a drug that was generating about $2.5 billion a month at the time, for the company.

MS. SIPES: Thank you. If you - I don't know if you're submitting any comments to the docket, but if you do and if you have any further thoughts on these issues, particularly, you know, authority for expanding the march-in rights, that would be of interest.

MR. LOVE: Thank you very much. I certainly will. That's it. Okay. Thank you.

MR. BYDLAK: Thank you very much for the opportunity to speak with you today about the taxpayer’s case for encouraging competition in the drug market. As Founder of the Coalition to Reduce Spending, I represent the interests of Americans nationwide who are concerned about the rising national debt and fiscal irresponsibility in Washington. In a time of ever-growing partisanship and political dysfunction, practical and bipartisan solutions can

very much be in short supply. And that's why we're very encouraged at any efforts to reform one aspect of the fastest growing part of the federal budget.

As I'm sure you're aware, in 1960 healthcare costs were just 5 percent of the gross domestic product. By 2015, they were nearly 18 percent, and on track to keep growing. Prescription drug costs were 10 percent of total healthcare spending, and in recent years their growth rate has outpaced that of all other healthcare services. When costs rise, it's the federal government that bears the largest burden, at nearly 30 percent. Federal involvement in healthcare is likewise projected to outpace other sectors in the near future, as more and more Americans join the Medicare rolls and otherwise age into federal programs. While the current political climate has shown how difficult it can be to make large-scale changes to U.S. healthcare policy, the Food and Drug Administration has a unique opportunity to encourage development of and access to cheaper generic prescriptions. By doing so, you can preserve patient safety, spur increased innovation and by extension reduce healthcare costs. Straightforward

steps like clearing out FDA's generic backlog would go a long way toward helping to realize drug savings. But, I'd also like to address one other means by which FDA can support affordable prescriptions, and that's by taking steps to discourage abuses of risk evaluation and mitigation strategies.

As you know, REMS were created to encourage -- ensure consistency in drug manufacturing, and thereby minimize potential risks to patient safety. However, in recent years, REMS increasingly have been used to make it more difficult for generic and biologic manufacturers to enter the marketplace, and have served to reduce competition and innovation rather than encourage it. We believe that in addition to being a clear violation of FDA's intent, REMS abuses have the side effect of increasing drug costs to consumers.

These abuses occur when brand name producers refuse to let generic competitors participate in shared safety protocols. In other words, pharmaceutical companies use their REMS as an obstacle to innovation under the implicit assumptions that only they can provide -- can safely produce the medications Americans

desire. In these instances, rather than fostering a diverse marketplace for consumers, REMS can serve as a tool for creating drug-specific monopolies. This monopoly power is reinforced by other means, such as refusing to let generic competitors have access to the biological materials necessary to test and prove that their generic versions are safe.

And the harm to consumers and taxpayers from these abuses is hard to overstate. A 2014 analysis showed that industry abuse cost the healthcare system over $5 billion per year. And again, $1.8 billion of these costs are borne by the federal government. Other analyses have found numbers as high as $14 billion in annual lost savings when generic drug production is stifled. And while allowing for healthy competition in the pharmaceutical marketplace has obvious benefits for American patients, improvements can come to our nation's public finances as well.

As one example, a 2013 analysis found that the ten-year savings from allowing just 11 biosimilars to enter the market would exceed $250 billion. And while there are costs like these that are seen, there are

many others that go unseen. For example, in an environment where brand name prescription drug manufacturers face less pressure from competitors, how many potentially lifesaving drugs do they not invest in because it's more profitable to litigate claims against generic competitors or otherwise work to maximize the profits from drugs they've already developed.

It's for these reasons that the Coalition to Reduce Spending is enthusiastically supporting current legislative efforts like the CREATES and FAST Acts, which offer paths to relief from bad faith REMS action on the part of brand competitors. It's critical, in our opinion, to remember that competition in the marketplace should mean pressure based on who develops the best prescription remedies, not from litigation and exploitation of the spirit of FDA's rules. While some may argue that these legislative solutions would encourage frivolous litigation against brand name manufacturers, the reality is that disputes of all kinds are already being litigated through the court system, and adding clarity to FDA's rules would reduce misunderstandings, not increase them.

These narrowly tailored proposals would give an affirmative defense for brand manufacturers against frivolous claims, while ensuring that REMS functions as intended -- to protect patients, not to defend anyone's bottom line. And, of course, less litigation would ultimately mean lower drug costs for consumers and the U.S. Government. We also believe it would be beneficial to taxpayers for FDA to provide further clarity on when the agency will waive single shared REMS requirements.

You know, we believe that you have a critical role to play in ensuring consumer safety, by taking proactive steps to ensure that your systems are not used to crush competition. You can also ensure the needs of consumers and taxpayers are considered as well. Americans rightfully want the government to spend less and provide for the best possible quality of life for its citizens. The FDA has an opportunity, in our opinion, to achieve both goals.

Thank you very much for the opportunity to address you.

MS. TOUFANIAN: Thank you for your

presentation. You referenced a number, I think, two or three different studies, one in 2014, a different one in 2015. I'd encourage you to submit that information to the docket for our consideration.

MR. BYDLAK: We will. Yes.

MS. TOUFANIAN: Great.

MR. BYDLAK: Thank you very much.

MR. MITCHELL: Good afternoon. I apologize in advance for not supplying my prepared remarks in advance for the panel. I'm Jack Mitchell. I'm the Director of Government Relations at the National Center for Health Research (NCHR). NCHR performs original health research to inform public policy and legislation. We also advocate for patients and consumers. We also have a -- we manage an informal coalition of two dozen nonprofit organizations which focus on public health issues. NCHR accepts no funding from pharmaceutical or medical device companies, so I have no conflicts of interest to report.

We agree with Commissioner Gottlieb's recent blog posting and subsequent comments that brand name companies are sometimes gaming FDA's regulatory rules

in ways that unduly delay generic drug approvals beyond the time frame that the law intended. Generic drug companies usually need 1,500 to 3,000 dosages of the originator drug to use for testing. Some companies are using regulatory strategies to deliberately block access to these needed testing samples. For example, branded companies might use restrictions they place in the commercial contracts or their agreements with distributors to make it more difficult for intermediaries in the drug supply chain to sell the drugs to generic drug developers. Or, brand products are sometimes subject to limited distribution, either through REMS or through the company's voluntarily adopted limitations. We believe that these longstanding hurdles need to be corrected or amended.

We also believe that it should be possible for generic sponsors to buy the branded products for testing at affordable prices. This is especially important since the most expensive branded drugs are making healthcare increasingly unaffordable for many patients and consumers. And of course, one of Dr. Gottlieb's stated goals here is to reduce high drug

prices.

The Commissioner also pointed out that besides limiting access to testing samples, some branded companies may be using the statutory default requirement to have a single shared REMS across both the branded and generic versions of a drug as a way to block generic entry. These single shared systems can be used to delay the entry of safe and effective generic drugs under the marketplace. This must also be corrected or amended.

Finally, we want to express our concerns about various mechanisms that have been used to extend patent protection on drugs, including the so-called pay for delay tactics. It is well-known that many of these mechanisms have ended up increasing, not reducing, the cost of treatments and provided relatively little benefit regarding access to safe, effective and affordable treatments available for patients, including children and patients with rare diseases.

So, in summary, the legislation popularly known as Hatch-Waxman, named after its two primary Congressional sponsors, over time has had a significant

impact on increasing both drug innovation and access to cheaper but effective generic drugs. For its continuing success, there needs to be a bit of a course correction. We have no specific suggestions, but just in summary I would like to point to some of the excellent suggestions made by Professor Carrier this morning, in his presentation. We would certainly concur with the idea of, if it's feasible, for FDA to consider requiring sample deposits to ensure they're testing for future availability for generic drug manufacturers.

We would also like, as Professor Carrier stated, to have REMS related and citizen petition abuses addressed. They are longstanding, and they violate both the spirit and intent of Hatch-Waxman. We urge, as you've already committed, to work with Congress and FTC and your other federal partners to curb these abuses, which, as I said, have been longstanding. Just finally, we hope FDA will follow and implement the Commissioner's recommended course of action to further improve this system for the future benefit of patients and industry alike. Thank you very

much for hearing my comments.

MS. COX: Good afternoon. My name is Ayeisha Cox, and I serve as a Policy Advisor to the not-for-profit Center for Lawful Access and Abuse Deterrence, also known as CLAAD. Our organizations works to reduce prescription drug fraud, diversion, misuse, and abuse while advancing consumer access to high-quality healthcare. CLAAD's funders include treatment centers, laboratories and pharmaceutical companies and are disclosed on our website at claad.org. Thank you for the opportunity to provide CLAAD's input on preserving the balance between encouraging innovation in drug development and accelerating the availability to the public of lower cost alternatives to innovator drugs.

The FDA can accelerate the development of generics using its current authority under the FDCA. For example, CLAAD recently filed a citizen petition detailing how the FDA should act once it has approved three oral immediate release or extended release long-acting opioid analgesics with abuse deterrent labeling with the same active moiety. In such event, the FDA

should mandate that all oral opioids without abuse deterrent properties with that active moiety and release profile be converted to an ADO within three years of the approval date of the third ADO. Otherwise, it should be removed from the market after a three-year period, if they have not been converted to an ADO.

Given that to date no generic opioid has received FDA approved abuse deterrent labeling, such action by the FDA would incentivize generic manufacturers to bring generic ADOs to market faster.

Additionally, protecting patient safety and encouraging the development of generics are not mutually exclusive, specifically for products with REMS. As you know, part of the REMS statute, medications carrying serious risks would not be allowed on the market but for REMS safety protocols. Therefore, REMS safeguards must be preserved.

Important safety risks that brand manufacturers mitigate through REMS should be equally addressed by generic manufacturers. If brand and generic manufacturers cannot agree on a shared REMS,

the FDA should identify the elements in the brand manufacturer's REMS program that generic manufacturers must meet. A REMS proposal that lacks these elements should be denied.

Under the statute, the FDA has broad authority to remove a drug with an unsatisfactory REMS from the market if it does not meet the elements required to ensure patient safety. This requirement of equal safety protocols is consistent with the policy the FDA established in its draft guidance on principles to evaluate the abuse deterrence of generic opioid analgesics. The guidance emphasizes that moving forward, generic drug manufacturers seeking approval of their product must ensure that the generic is no less abuse deterrent than its brand counterpart on the market.

Lastly, we also encourage the FDA to use its authority to require product specific REMS when appropriate, instead of removing a drug from the market that meets an otherwise unmet need. For example, the FDA could have required a product specific REMS for the soon to be removed extended release oxymorphone product

to better manage the risk associated with a product while also ensuring its availability to patients who need it.

Thank you again for this opportunity, and please contact CLAAD if we can be of any service to you. Thank you.

DR. UHL: I did not attend the most recent public meeting related to opioids. And I'm curious or not if CLAAD was there, and if you submitted comments to the docket related to the whole abuse deterrent opioids and REMS and all that kind of stuff.

MS. COX: We were not in attendance at that public meeting.

DR. UHL: Okay. Thank you.

MS. COX: Thank you.

MR. KNIEVEL: Hello. Thank you to the panel for the opportunity to present on the vitally important issue of lowering drug prices. Public Citizen is a national consumer advocacy organization with more than 400,000 members and supporters. We advocate in an array of issue areas to advance the public interest, including insuring prescription drugs meet high safety

and efficacy standards and are made more affordable, both in the U.S. and abroad.

In our view, the root problem of high U.S. drug prices is the monopoly power of the pharmaceutical industry. Government granted monopolies provide incentive for prescription drug corporations to engage in a range of abusive behaviors, from fraudulent reimbursement schemes to price gouging to efforts to inappropriately extend monopolies through evergreening, REMS abuse and pay for delay deals. I will use the remainder of my time to identify a menu of existing policy options, as well as suggested policy reforms for your consideration.

Because our nation's medicine affordability crisis derives from the pharmaceutical industry's monopoly power, the first step is for policy makers to stop expanding monopoly powers. For instance, proposals for a new six months' exclusivity period for all indications on an existing medicine, when that medicine gains approval for a new orphan indication, should be rejected. We do not have a scarcity of orphan drug development in this country, and the new

monopoly period would increase prices and provide incentive for abuse. We are encouraged by the planned GAO study into the Orphan Drug Act.

When drug corporations abuse their government granted monopolies by price gouging consumers and taxpayer funded government health programs, the U.S. Government should exercise its existing authority to remedy the abuse. This is especially the case when it comes to U.S. Government funded biomedical inventions. 35 U.S.C. 203 provides federal agencies with the authority to march-in on U.S. Government funded inventions, to allow for generic competition when a patent holder fails to make a product available on reasonable terms. When U.S. taxpayers are paying more than other wealthy countries for an invention developed through taxpayer dollars, it is inherently unreasonable. When that is the case, NIH, DOD and other agencies should exercise march-in.

In cases of drug industry price gouging of government health programs, 28 U.S.C. 1498, also known as government use, is another tool currently available to remedy drug industry monopoly abuses. For example,

Louisiana Secretary of Health and Human Services Rebecca Gee recently wrote experts to explore the viability of utilizing 1498 to expand access to treatment for people with Hepatitis C. Public Citizen submitted joint comments in support. Patients in Louisiana and other states are facing treatment rationing, such as requirements to get sicker before they'll be granted access to treatment. From a public health perspective, this is irrational. And from a moral perspective, this is unconscionable. When drug industry profiteering prevents access to lifesaving medicines, the government should use 1498 to allow generic competition.

Generic industry consolidation impedes competition, increasing potential for off-patent no exclusivity products that face no competition to allow for sharp price spikes. FTC should work to prevent mergers and acquisitions in the generic drug industry to ensure that we have the robust competition necessary for a well-functioning generic drug marketplace.

Rather than expanding the monopoly power of the pharmaceutical industry, legislators should also

seek to curb monopolistic abuses to lower medicine prices for consumers, taxpayers and government health programs. FTC estimates that backroom pay for delay deals cost consumers and taxpayers $3.5 billion annually. The FTC should continue to aggressively prosecute such deals, and legislators should pass the Preserve Access to Affordable Drugs Act, introduced by Senators Klobuchar and Grassley, to help curb this abuse.

Pharmaceutical abuses of REMS inappropriately extend monopolies and delay competition, costing consumers and taxpayers $5.4 billion annually. Legislators should stop these abuses through bipartisan reforms, like the CREATES Act and FAST Generics Act.

IMSHealth's recent study of biosimilars in Europe found that biosimilar competition lowers prices and increases patient access to the whole product class, even beyond the biosimilar and its reference products. The legislators should reduce the period of biologic's exclusivity from 12 to 7 years, as has been proposed in legislation. Such legislation has been scored to save the federal government around $7 billion

over a ten-year period, and it's reasonable to anticipate that the rate of accrual of such savings would increase in later years.

Public Citizen's analysis found that from 1991 to 2015 the pharmaceutical industry paid more than $35 billion in civil and criminal penalties to states and the federal government. Fraudulently overcharging Medicaid and other government health programs was the most common violation resulting in such payments. But these fines and payments are not enough to curtail the abuse. When drug corporations abuse consumers and taxpayers through fraudulent and other criminal behavior with relation to a drug, the government should stop providing market protections to the corporation with relation to that drug. The Public Citizen supports language in the Improving Access to Affordable Prescription Drugs Act, which would do just that. The prescription drug industry spends several billion dollars annually on direct to consumer advertising, often in efforts to steer consumers to more expensive treatment options when lower cost effective alternatives are available. We support language in the

Improving Access to Affordable Prescription Drugs Act that would remove special tax incentives for DTC advertisements, helping to make treatment decisions more rational and provide savings to consumers and taxpayers.

Finally, as policymakers seek solutions, they should watch out for reforms that would have no or negligible impacts, especially when they may have negative unintended consequences. Generic drug priority review voucher proposals represent a fundamental misunderstanding between the different ways the brand name drug market and the generic drug market operate. A generic PRV program would provide little to no incentive to induce competition for sole source off-patent small market drugs, and would not prevent Shkreli style price gouging or lower prices.

The House passed user fee reauthorization bill includes in Section 808 a new 180-day exclusivity period for so-called first generics. Such a mechanism would not achieve the stated goal of increasing competition for otherwise uncompetitive markets, and even further that 180-day exclusivity period would

delay more robust competition for other products and as a consequence keep prices higher for longer, increasing drug prices. FDA research has shown the dramatic price reductions only occur when there are two or more generic competitors on the market. We were pleased to learn that on Thursday the White House shares Public Citizen's concern with this provision.

Once again, I want to thank you for the opportunity to provide these remarks. We look forward to providing written comments on these and other issues relating to lowering drug prices, as well as working with you and other policy makers towards our shared goal of ensuring Americans have access to affordable medicines that they need to lead healthy and productive lives.

MR. FLANAGAN: Thanks for your very specific comments. When you do submit comments to the docket, the comments focusing on how, at least, FDA can leverage its existing authorities to -- and develop administrative and regulatory reforms are probably the ones that are most immediately useful to us.

MR. KNIEVEL: Yes, sir. As was previously

commented, the call for testimony at this spoke to the generic marketplace generally. So, we wanted to provide comments broader than that specifically.

MR. FLANAGAN: Thank you.

MS. DICKINSON: Do you have a working definition of price gouging?

MR. KNIEVEL: I think that is generally understood to be profiteering behavior, where companies abuse their either government granted monopoly or de factor monopoly to charge unduly high prices. I could -- we could speak to that further in our written comments, though.

MS. SIPES: Thanks for your comments. You mentioned the Bayh-Dole march-in rights and also the government use law, as did a previous speaker who, if I understood correctly, suggested that march-in rights could be extended to any product regulated by FDA. Do you have a reaction to that?

MR. KNIEVEL: I believe that those rights are limited to government funded inventions, in a particular stage of funding in the drug's development. We would be very interested in that law being expanded

to include funding for more stages of development. But, that is my understanding of the statute.

MR. FLANAGAN: Thank you.

MR. KNIEVEL: Thank you.

MS. WILD: Hi. Good afternoon. My name is Nellie Wild, and I would like to thank you for the opportunity to be here to provide comment. I do want to note that I am delivering comments prepared by Phyllis Greenberger, who is the Senior Vice President for Science and Health Policy for HealthyWomen, the nation's leading independent, nonprofit health information source for women.

A priority for HealthyWomen and the women's health community in general is to increase the development and availability of life-enhancing medicines where the safe use of these innovative drugs and biologics is paramount. However, we also support expanded patient access to lower-cost generic drugs and appreciate the Food and Drug Administration's effort to implement policies that will advance both goals.

Before joining HealthyWomen, I served as President and CEO of the Society for Women's Health

Research, SWHR, where I spearheaded an initiative in 2009 with the Institute for Alternative Futures. Together we hosted a stakeholder workshop to chart the optimal development and application of FDA's Risk Evaluation and Mitigation Strategies, or REMS, program. The effort resulted in the publication of a detailed report, Optimal Futures for Risk Evaluation and Mitigation Strategies, in 2010.

My background enables me to reflect upon the needs of women when designing and implementing REMS policy, including recognition that women face unique drug safety challenges that REMS can address, such as preventing fetal exposure to teratogenic medicines, and women are also disproportionately affected by diseases and conditions like multiple sclerosis which are effectively treated with medicines approved with REMS requirements.

Going back to 2009 when the REMS program was still in its infancy, there was already an interest in supporting the development of generic drugs subject to REMS, due to the recognition that the number and variety of these lower-cost medications would increase

significantly in coming years. Accordingly, the stakeholder meeting focused on the implications of REMS requirements for generic drug developers, leading to the call for policies that would assure branded and generic drug manufacturers are held to the same standards when implementing tightly controlled restricted distribution programs.

This assessment was based on examining the initial design of the iPLEDGE risk management system for the acne treatment, isotretinoin, a potent teratagenic drug, where insufficient safety controls in the first year of operation of this risk management system resulted in 122 unplanned pregnancies. Towards this end, the workshop attendees and the resulting report called on FDA to develop quantitative methods to evaluate or validate a generic's risk management program and to develop a contemporaneous monitoring and enforcement policy.

Seven years have passed since the publication of the Optimal Futures for Risk Evaluation and Mitigation Strategies report and during this time the REMS program has matured. Part of the evolution has

been the approval of a number of generic drugs subject to REMS safeguards. Based on the latest information from FDA's website, there are now 42 REMS with elements to assure safe use, ETASU, the most restrictive types of REMS. Of these REMS with ETASU, 11 are shared systems where both branded and generic versions use the same REMS procedures to manage the risks of potentially dangerous drugs.

For the nation's over 160 million women, this development represents an important step forward. According to FDA's estimates, Americans save $8 billion to $10 billion a year by purchasing generic drugs rather than brand-name medications. Yet, REMS exist because some medicines can cause life-threatening complications and terrible birth defects, which is why it is critical for FDA to preserve the integrity of REMS and its Elements to Assure Safe Use requirements, including restricted distribution systems, even as the agency works to approve more lower-cost generic options of branded REMS drugs.

In examining the 42 drugs or drug classes requiring REMS with ETASU, there are some common safety

concerns. The largest number of REMS medicines marked with ETASU requirements cause birth defects -- nine drugs or drug classes -- a key concern for the women's health and reproductive health communities. Additionally, seven drugs or drug classes prevent diversion, overdose and misuse, four address hepatotoxicity and hepatic injury, and four prevent life-threatening infections. Therefore, one possible solution to accelerate the availability of drug samples is for FDA to develop and publish customized guidance for medications based on the specific safety risk, for example birth defects, the REMS with ETASU designed to mitigate.

This concept does not work for all medications requiring ETASU but for those where there is a common safety challenge. Providing an apples to apples roadmap for branded and generic drug manufacturers to follow could streamline the process, saving time for the companies and costs for the agency.

HealthyWomen commends FDA on its leadership in implementing the REMS program and for continually working to improve this drug safety system based on

patients' needs. Thank you for the consideration of these comments.

MR. REYNOLDS: Good afternoon. I'm Ian Reynolds, representing the Pew Charitable Trusts. Pew is a nonprofit nonpartisan research and policy organization. One of our focus areas is the challenge of rising drug spending.

Hatch-Waxman has largely been a success, giving manufacturers incentives to develop new drugs while facilitating competition and access to medications. The law has driven innovation and created a robust generics market. The savings from this competition is estimated in the hundreds of billions of dollars per year. However, there are areas where the law may not be working as intended, and some practices can inhibit the availability of lower cost generics and undermine competition. Additional efforts to remedy these challenges may be warranted.

It's important to recognize that some barriers to competition lay outside the scope of FDA's current authority, and changes may require Congressional action. As a baseline for understanding the

pharmaceutical market, FDA must have reliable data on the status of approved products. The version of the FDA reauthorization act that passed the House would require that sponsors inform FDA whether approved drugs are currently marketed. If enacted, we encourage FDA to require this information be provided to the agency in a standard format, so it is easily usable and can be made public.

There are three keys issues related to Hatch-Waxman we would like to comment on today. First is the use of risk evaluation and mitigation strategies, or REMS, to delay generic entry. Generic and biosimilar developers can encounter challenges in accessing sample brand drugs, subject to REMS, that include elements to ensure safe use. This can inhibit generic developers' ability to conduct bioequivalence testing. In addition, brand and generic makers of drugs with these kinds of REMS are required by law to participate in a single shared REMS protocol, unless FDA waives the requirement, which would allow for separate REMS. However, some innovator manufacturers may make it difficult for generics to participate in a joint REMS

protocol. Each of these can delay access to lower cost products.

We appreciate FDA's acknowledgement of these challenges, and signaling that it may use its authority to waive the shared REMS requirement more often. However, waiving this requirement also has the potential to create inefficiencies. For example, participating pharmacies and prescribers may need to spend additional time enrolling in or training on multiple REMS systems. We urge FDA to exercise this authority judiciously when waiving the shared REMS requirement. We suggest the agency do so in a way that creates parallel systems and minimizes any potential for discrimination between the uptake of the brand and generic products.

While FDA's authority is limited, and proposals in Congress would take further steps to stem abuse of REMS, we note that current law prohibits drug makers from using the REMS to block or delay the approval of a generic application, or to prevent a generic developer from participating in a shared REMS program. While we're not aware of FDA ever using its

authority in this area, we recommend the agency take enforcement action when it's appropriate.

The second issue of concern is the abuse of the citizen petition process. Citizen petitions can be useful when they contain legitimate recommendations or raise valid scientific concerns for FDA consideration. The citizen petition process has often been used to request the FDA take action relating to pending applications for generic drug approval. However, citizen petitions have the potential to delay generic approval and reduce competition. The majority of citizen petitions related to generic applications are ultimately denied. This suggests that many are meritless.

Although FDA has met statutory deadlines for reviewing petitions related to generic applications, its 2015 report notes that the agency has had to redirect resources from other work in order to do so. That same year, FDA reported that two generic applications were delayed due to citizen petitions, and in one case brought by the FDC earlier this year the commission alleged that abuse of the citizen petition

process to delay access to generics of just one drug resulted in hundreds of millions of dollars in additional cost.

We recognize FDA's recently implemented changes to help ensure that citizen petitions are not improperly used to delay approval of generics. We recommend that FDA continue to monitor potential abuses of the program, including establishing procedures to identify when manufacturers or their proxies frequently submit petitions that lack valid concerns and are routinely denied, and to make this information public.

Our last point focuses on the FDA's unapproved drugs initiative. This initiative has an important goal, but it has the potential to drive up prices by creating exclusivity to already widely prescribed medications. The grant of exclusivity should be commensurate with the costs to the sponsor conducting new research and submitting an application. We encourage FDA to conduct and publish an analysis on the scope of new clinical research on drugs for which exclusivity has been granted under this initiative, as well as evaluate how the prices for these drugs have

changed after receiving exclusivity.

Finally, we recommend FDA not focus on importation or changing its quality or safety standards in order to speed access to generics. These approaches may pose risks to the patients, and have other intended consequences. Thank you.

DR. UHL: Thanks. Under your first item, related to REMS, you mentioned that the FDA should consider taking enforcement action. Could you expand upon that, and under what circumstances you would suggest to us that we do that? And then what kind of enforcement action?

MR. REYNOLDS: FDA -- if FDA believes that REMS are being used to delay generic access or approval, you know, that's a decision that FDA can make internally. But, if there are situations perhaps where the law is not clear, that's something that could be discussed further with Congress as well.

MS. RINKER: Good afternoon. I am Martha Rinker. I'm the Vice President for Public Policy for the National Organization for Rare Disorders (NORD). And we're a unique federation of voluntary health

organizations dedicated to helping people with rare orphan diseases, and assisting the organizations that serve them. NORD is committed to the treatment and cure of rare disorders through programs of education, advocacy, research and patient services. And I want to give you a few basic facts before I present NORD's three points on Hatch-Waxman.

There are more than 8,000 known rare diseases. There are 30 million Americans that are affected by these rare disorders. 50 percent of them are children. And as of December 31st, 2016, there have been 549 orphan indication approvals for 449 drugs since the Orphan Drug Act was enacted in 1983. And another very important piece of this is many patients with rare disorders have no approved therapeutic treatments for their disorders, and receive off-label therapies.

Now, with that landscape in mind here are the three points that NORD would like to present today. NORD supports the robust development and availability of generic products, once an innovator's Orphan Drug Act incentives have run their course. We appreciate the need to balance product development, innovation and

public access to lower cost alternatives. NORD supports efforts by the FDA to develop processes for expediting the generic drug approvals, such as proposals to provide early guidance for applicants.

And finally, NORD asks the FDA to be sensitive to the patients' needs. Drugs should be available and affordable to patients when they require them. And with that, I end my brief statement and thank you for the opportunity to present those points.

MS. TOUFANIAN: With respect to your last point regarding -- Keith agrees with my question. He doesn't know what I'm going to say. Could you elaborate a little bit more on your last point, regarding consideration of the patient? And if there are specific policies or steps that the agency can take to address or incorporate that specific concern into our regulatory practice.

MS. RINKER: Well, I think it's knowing the patient journey and taking in the patient's viewpoint on access to care, I think. We can address that more in our -- on our written statement, though.

MS. TOUFANIAN: Please do. Thank you.

MR. FLANAGAN: I was going to ask the same question.

MS. RINKER: Okay.

MR. FLANAGAN: Thank you.

MS. RINKER: Anything else?

MR. FLANAGAN: Thanks.

MS. RINKER: Okay. Great. Thanks.

MR. MITCHELL: Thank you. Good afternoon and thank you for this opportunity to present today. I am David Mitchell. I am President and Founder of Patients for Affordable Drugs, a national patient organization focused exclusively on policies to lower prescription drug prices. To maintain our independence, we do not accept funding from any organizations that profit from the development or distribution of prescription drugs.

Since we launched our effort five months ago, we have heard from more than 7,000 patients from all over America. They've shared their stories of skipping doses, cutting pills in half, choosing between food and the drugs they need.

More specifically to the discussion today, I am a relapsed cancer patient with multiple myeloma, an

incurable blood disease. Drugs are keeping me alive, literally. So, the importance of innovative, affordable drugs is not theoretical to me at all. It truly is a matter of life and death. I am very grateful for the work of the FDA and for the drugs produced by the science and research sector in our country. But lifesaving drugs don't work if people can't afford them.

A week ago, I sat in an infusion room for five hours receiving a two-drug combination -- thank you for those drugs, by the way -- priced at more than $20,000 per treatment. I will have this treatment 22 times this year. $450,000 or so of drugs is what's keeping me standing here right now.

Prior to this drug regime, however, I took Revlimid for five and a half years, and I participated in Revlimid's Risk Evaluation and Mitigation Strategy program, of course made by Celgene. I obtained my drugs only from specific specialty pharmacies. Each month, I received counseling on the risks of the drug, and I participated in a survey designed to remind me of those risks and make sure I understood them. The most

dangerous risk with Revlimid -- the generic is lenalidomide, it's a derivative of thalidomide -- so the most dangerous risk is birth defects. The counseling consisted of a nurse reading a list of cautions to me. The survey was an automated phone call, -- press one for yes and two for no. The whole process took five to ten minutes. It could easily have been duplicated by any generic manufacturers. It truly wasn't rocket science.

Of course, during the same period, Celgene was hiding behind its REMS program to delay versions of the drug, refusing to give samples to generic drug makers so that a cheaper generic could come to market. Here's what that meant for me. My out of pocket cost for Revlimid went up by 500 percent, from $42 a month to $250 a month by the time I had to stop taking it because of side effects. Another side effect of Revlimid is blood clot. I had one. The docs changed me up.

The retail price for a four-week cycle of Revlimid during that period jumped to more than $500 per capsule. Now, I'm lucky. At the time, I had good

employer-provided insurance. But others aren't so fortunate. The median out of pocket cost for Medicare beneficiaries taking Revlimid is $11,500 per year, almost half their annual income. Now, that's the impact of REMS and restricted distribution system abuse. Patients are forgoing their medication. They're spending their retirement funds and their kids' college savings to afford drugs when a generic competitor sits around the corner.

I have three points I'd like to make today to the FDA. First, thank you to you and to Scott Gottlieb. I applaud you for clearly articulating that the agency will not consider it a violation of REMS or any other rules for a brand pharmaceutical corporation to allow another manufacturer to perform necessary testing to create an equivalent generic drug. Contrary to what one of the gentlemen said from PhRMA or BIO, you sent a letter to Celgene, told them to release the samples. They refused to do so. It is very difficult for me to imagine that any brand name company the size of, for example, Celgene, putting out a dangerous drug -- it is a dangerous drug, it requires a REMS -- would not have

adequate indemnity insurance to protect them from lawsuits from patients, or anyone else who might touch the drug or somehow be hurt by the drug. So, the idea that not having -- being concerned about lawsuits seems to me to be beyond the pale.

Secondly, as a patient, I understand that safety is absolutely paramount. A single shared REMS is efficient for patients, doctors, and regulators. But bad actors are currently abusing the current system. The FDA should forbid companies from declaring information about REMS to be proprietary. After all, REMS are a public good. They are not intended to protect corporate monopolies. FDA should collect and issue best practices for REMS so all manufacturers -- now and in the future, brand and generic alike -- can draw upon previous learnings and easily set up systems. If a drug corporation like Celgene refuses to share REMS information with a generic manufacturer, the FDA should use its authority to waive the requirement for a single shared system.

Finally, the FDA should take additional action to ensure generic companies can obtain samples for

testing. If the FDA does not have the proper resources or authority to require the provision of samples, perhaps joint action with the FTC could be undertaken to stop this anticompetitive behavior. Most importantly, where the FDA doesn't believe it has sufficient authority to stop these abuses, I urge the agency, on behalf of patients like myself and others, to request immediate Congressional action. I believe the FDA should be explicit in support of solutions such as the bipartisan CREATES Act and FAST Generics Act, which aim to correct these distortions of the law.

And I thank you very, very much for the opportunity to come and talk to you about my personal experience, and how it reflects on the policies of this country. Thank you.

DR. BAKER: I'm Jim Baker, and I'm CEO of FARE, which is Food Allergy Research and Education. It's the organization that represents the 15 million Americans with food allergy. I've also been an allergist for over 35 years, developed drugs in the military, academia, large pharma and biotech. So, I have a broad perspective on generic markets.

I'd like to focus today on the epinephrine auto-injector market, which is a remarkable microcosm of all the issues related to generic substitution in the U.S. This market is very important to our members, because it involves a lifesaving medicine that they all need. Unfortunately, it's been manipulated and competition has been limited by several moves, and this has resulted in literally billions of dollars of excess cost for Americans.

One of the things we'd like to do is see more competition in this area, and we applaud the FDA's recent quick approval of the Adamis auto-injector, which along with the reintroduction of the AUVI-Q and the Impax Lab's generic device give consumers more choice. However, the cost of these devices still remains very high, and because of insurance changes more and more families find this untenable. And so, FARE would like to have even more competition in this space, and I'd like to focus on three options to encourage this goal.

Because epinephrine administration requires a device drug combination, there are unique regulatory

issues. One of the marketing companies has been able to argue that the auto-injector devices are not equivalent with very small differences, even their color simply being the difference, despite the devices all working. As a physician who has cared for allergic patients, I believe that almost anyone can be taught to use almost any device. And remarkably, patient choice in this is very divergent. So, no one device is really better than another.

If another safeguard is needed to assure that the substitution is safe, it could be done as it's done in Canada, where the pharmacist is required to explain the device. And in Canada, a prescription is not even required for this device, and the cost is one-sixth of what it is in the United States.

We also believe that references like FARE's website, that provide instructions for all of the approved devices, could help in this. We strongly encourage rapid approval of any device that's currently awaiting FDA review. Several devices in this area were rejected for what appeared to be relatively minor issues, and we would hope that you could also

facilitate that.

Finally, there are four auto-injectors in the European market that are not available in the United States, and help result in a much lower out of pocket cost in the EU. These are high quality devices, but they've not been brought into the U.S. because of regulatory hurdles. And even though they compare favorably in size and ease of use and accuracy, they would require substantial regulatory findings to get into the U.S. We suggest that the FDA allow the facilitated importation of these devices into the U.S., in a manner similar to shortages of cancer drugs or vaccines, especially until the market stabilizes.

We also urge the FDA to harmonize regulatory approvals with the EMA to facilitate the entry of these products. We want to really emphasize that the excess cost of generic products prevents true innovation in the pharmaceutical space. Every dollar spent on epinephrine that's not necessary is a dollar that cannot be used to develop new therapies that could prevent life-threatening allergic reactions. While in the short term we want better access to auto-injectors

for allergic sufferers, our real hope is a future where they won't require epinephrine at all.

Thank you.

DR. UHL: Thank you very much. I wonder if you might elaborate a little bit, and especially in your written testimony, about the differences in the auto-injectors, or other types of drug device combinations. So, even in your patient population, where you have, one, life-threatening patients with anaphylaxis who would require an auto-injector, and, two, what you kind of concluded with -- individuals who are allergy sufferers, which is obviously not necessarily life-threatening situations, but where there still might be the need for medications that are drug device combinations. So, do you have any thoughts about permissible differences, differences in different scenarios? Along those lines.

DR. BAKER: The most important aspect of this is the patient actually uses the device. And there have been recent studies that have shown that 50 percent of patients who don't give epinephrine to themselves never get it on the way to the hospital, or

even at times in the emergency room. So, getting compliance with the patient is most important.

All these devices are a little bit different, and that's usually in the way the injection occurs. Some give a spring that gives a hard bash. Others give sort of electronic injection that delivers the drug. And different patients like different routes. So, in fact, patient choice is most important here. So, we would like patients to have more choices. And since all these devices have been shown to deliver the drug effectively, they can't be approved without that, we feel that all of the options are viable. And I'll put more of that in our written commentary. Thank you.

MR. SPERLING: Good afternoon. My name is Andrew Sperling. I'm the Director of Legislative Advocacy for the National Alliance on Mental Illness (NAMI). I want to thank you all for giving me this opportunity, and thank you for the long day you've had sitting up there listening to all these inputs. So, NAMI is the nation's largest organization representing people living with serious mental illness in their families. We place a high value on accessing

treatment, to innovative therapy to treat disorders, such as schizophrenia, bipolar disorder, major depression, severe anxiety disorders.

The key thing for all of you to understand, and hopefully many of you know this, the therapies we have available to treat these disorders are not disease-modified. They're largely palliative, helping individual patients control their symptoms so they can reach some modicum of recovery and higher functioning.

We do not have disease-modifying therapies to actually change and allow people to get by without any treatment at all. And that's what we're yearning for. But, that breakthrough therapy that would really be a game changing therapy, will allow someone to never experience an episode of acute psychosis or acute mania or severe depression. Enormous public health burden -- close to 40,000 suicides every year related -- 90 percent related to untreated mental illness. So, we have a long way to go.

But, we also believe -- place a high value in incremental improvements. So, for example, a new antipsychotic medication that has no weight gain

associated with it is something that's of high value to patients. The side effect profiles of some of these medications are very challenging, particularly when you have to take them, in many cases, for the rest of your adult life. So, we value both that breakthrough therapy that we're lacking but also support incremental improvements. We have a long way to go.

But there's a good story to tell here, in terms of the value that Hatch-Waxman has meant for helping people access treatment to treat disorders such as schizophrenia, bipolar disorder and major depression. As you've heard earlier, the value of generics to the overall system -- $253 billion in savings in 2016 alone, according to QuintilesIMS data. We actually have fairly good data on what those savings has been across the therapeutic categories, to treat serious mental illness.

For example, of the top ten therapeutic areas in which there is data on the savings to the overall system for serious mental illness, four of them are therapeutic categories related to serious mental illness -- the top being depression, with savings of

close to $37 billion. Number four, anxiety disorders at $22 billion. Number five, bipolar disorder, at $18 billion in savings. And number eight, schizophrenia at $16 billion in savings. So, this is where -- if there's any case where Hatch-Waxman has been a value in bringing savings to the system, it's in medications to treat serious mental illness.

So, we have just a few brief recommendations for the FDA, of what you can do to improve on this record of success with Hatch-Waxman. Number one, eliminate the backlog and support development of quality applications. And I think Commissioner Gottlieb laid out what the agency is going to be doing on that this morning. We believe that's very much a positive step that the agency could really move out front on this.

The other critical piece -- beyond your control, but many of us as advocates in the room -- to push Congress to timely reauthorize all of the user fee agreements that provide the important resources that you need to get that job done. And many of the patient advocacy groups -- hopefully many of them that are here

talking to you today -- are supporting that effort. That got through the House earlier this week -- last week -- and we hope will have success in the Senate very, very soon.

Number two, prioritize review of ANDA applications for medications to treat mental illness. You did -- I think the agency did a pretty good job with the large number of antipsychotics and antidepressants that have gone off patent over the last decade. And we want to see that continue, as products lose their patent protection and generics become available to lower those prices.

Number three, FDA can further explore potential barriers to development of medicines to treat serious mental illness. This is an enormous challenge. Drug discovery in the realm of psychiatry is really probably the most challenging area. We don't have a biomarker for schizophrenia. It's very, very difficult to do animal testing. You can't actually ask a lab rat if they're feeling psychotic, if they're feeling depressed, if they're feeling anxious. So, big challenges in this arena. The actual clinical trials

themselves cost significantly more than in other therapeutic areas. So, we need the FDA's help to validate biomarkers. Work with your colleagues at the NIH to develop innovative trial designs. Use of patient-reported outcomes to spur innovation and foster competition. There's a lot we need to do to spur the innovation and that's really, quite frankly, what our members who live with these disorders, and their family members, every day are desperate for -- is that breakthrough therapy. No one is content with the treatments we have available to treat these disorders, and we need both the incremental improvement and the breakthrough therapy.

So, thank you for this opportunity to talk to you today. And if there's any questions, I'll be happy to answer them.

MR. FLANAGAN: Thanks, Andrew.

MR. SPERLING: Thank you.

DR. WHITLOCK: Thank you. Pleasure to be here this afternoon. Thank you all for hosting the meeting. I'm Rodney Whitlock. I am a Policy Advisor to the Campaign for Sustainable Drug Pricing. Let's see if

this works. Okay. The campaign is a project of the National Coalition on Health Care Action Fund, nonprofit and nonpartisan organization dedicated to improving the healthcare system and keeping it affordable. The campaign's mission is to foster and inform the debate on sustainable drug pricing, and we are working to raise the profile of this issue and develop market-based policy solutions developed around transparency, competition and value.

This is our set of logos. Rather than go through all of those, just to say we're a broad stakeholder group including insurers, providers, inclusive of health systems and hospitals and physicians, inclusive of patient advocates, large employers and employee groups. And they're all subject generally to the consequence of rising drug prices, which draw them together to talk about the subject.

This is an example of data that speaks to the concern that our members face when drug prices outpace other cost growth in healthcare. The problem that we'll be talking about today, and particularly pulling off of the drug competition action plan that FDA

described in the blog by Dr. Gottlieb, goes to the competition issue, and particularly towards REMS. And again, that we have seen competition work to the advantage of the system, now saving, in this case, $1.67 trillion.

Generic competition, our concern is, is too often blocked by de facto extensions and de jure monopolies. Specifically, as noted in the blog post, that occasionally the rules are gamed or misused. And in Dr. Woodcock's testimony, that some branded manufacturers feel that it is their duty to their stockholders to delay competition as long as possible. As a coalition, our concern remains with what we see as affirmative barriers to competition, created under the existing regulatory regime. The problem that we are focusing on, and particularly want to raise for the purpose of this conversation, is with the REMS process.

And pulling from the blog post, you know, that the use of REMS and non-REMS to restrict distribution, and access to samples required for comparative testing is problematic, along with the intentionally prolonged negotiation over single shared REMS, that the blog post

itself pulled out as an issue. A study by the Association for Accessible Medicines found that restricting distribution network abuse costs the health system as much as $5.4 billion annually.

Competition is a good thing. Competition drives down costs. One of PhRMA's own studies found that the price of generic medication falls 66 percent during the first year of competition coming onto the market. And that increased generic competition creates significant savings, and reduces barriers to taking medicine at the appropriate intervals. We know there's no silver bullet in the area of drug pricing. There's no magic wand to wave here. It is not -- in any way do we say here's the fix, take it from here. It's a set of steps that you would take to try to improve upon the existing system. And the opportunities are out there currently.

The action plan suggested by Dr. Gottlieb is a step in the right direction. We also see that the FDA does have constraints on what is their legal authority -- what they're able to do. We know that there are pieces of legislation currently before Congress, the

bipartisan, bicameral FAST Generics and CREATES Act that would help deliver on the course charted by Dr. Gottlieb in the drug action plan.

And so, to close, on behalf of us, I'd like to put this in context for you all in what the legislative process needs to produce. With any good fortune, we'll be done with the user fee acts imminently, one would hope. Okay. After that, turning to other subjects, particularly addressing the REMS issues, the opportunity is there. The legislative process works best when the legislative branch works with the agencies to agree upon legislative language that is delivered into law that can then ultimately be turned into something that could be implemented by the regulatory agency. That working together is the opportunity that you have that Dr. Gottlieb has already launched. And we look forward to seeing that done, in the case of the REMS process, to something that will benefit the consumers generally. I'll stop with that.

MS. ABRAM: I have one. Hi, Rodney. Thank you for your comments.

DR. WHITLOCK: I was hoping your microphone

would break.

MS. ABRAM: Nope. It's working loud and clear. I just wanted to encourage you, and to carry this back to the extent that the Campaign for Sustainable Drug Pricing has suggestions or areas that you would recommend to the agency to look at, within our administrative authorities. We would appreciate that feedback as well, in addition to what you might suggest with respect to legislative opportunities.

DR. WHITLOCK: Certainly. And if I can turn the question, where you see the extent of your authority ending -- where counsels are telling you uh-uh, you know, getting that out for the purposes of both folks like us but certainly folks on the Hill, is valuable.

MS. ABRAM: Received. We're in a listening mode today, and want to encourage lots of comments in the docket.

DR. WHITLOCK: Yes, ma'am.

MS. ABRAM: Thanks, Rodney.

MR. BALTO: Good afternoon. I'm David Balto. I used to work with Markus at the Federal Trade

Commission, helping to lead efforts in the -- against anticompetitive conduct in pharmaceuticals. I am a public interest antitrust attorney, and I lead the Coalition to Protect Patient Choice, a coalition of consumer groups concerned about healthcare competition issues. Here's the best news of your afternoon. I'm going to do this in 5 minutes, even though you've given me 15. If you can turn to slide number seven. You know, as somebody who works -- maybe it's the slide before that. It's a quote by Robert Bork. The -- it's -- keep going. It's important when we look at -- I wanted to start off with three basic principles that I think should guide the way you look at -- there, that's the slide.

This slide in fact -- there should be a big marble block in front of the FDA, and Judge Bork's quote should be on that block. And every FDA regulator should see this quote before they walk in every day of work. Predation by abuse of governmental procedures, including administrative and judicial procedures, presents an increasing danger to competition. He said that 40 years, and never is it more true than at this

agency than at this point in time.

You know, I work generally in healthcare competition markets. And no market functions quite as effectively as the generic drug market. But, there has to be a generic drug market before that competition will occur. And the process of FDA regulations provides a tremendously fertile medium for the abuse of the regulatory process, to keep that competition from ever occurring. You know, regardless of where you are in the political spectrum -- abuse of the regulatory process, acquiring monopoly power through that abuse -- is the most pernicious form of monopoly power.

Why? Because if Google or Microsoft acquire monopoly power by inventing some better product, we don't worry quite as much. Because someone else is going to arise and develop a better product, and develop a better product and displace them as the monopolist.

But when someone secures monopoly power from the abuse of the regulatory process, no market force can displace that. When the FDA decides that somebody drawing a line across a tablet is something that's

worth putting in the Orange Book, there's nothing that a soul in this universe can do to go and permit the generic firm to enter the market. That's why, as a first principle, the agency and Congress needs a heavy dose of regulatory humility. Because wherever you put that regulatory spectrum, the greater powers that are exercised -- the powers that are exercised that aren't supervised, especially the powers that are exercised where no one gets to see what's happening, that's the best medium for monopoly power. John D. Rockefeller couldn't even dream of that.

Second, let's talk about innovation. Alex Brill had a great comment. Innovation is not contrary to the growth of the generic market. In fact, they are complements to each other. And when the regulatory process is abused, it's not only stopping these generic firms from entering the markets. It delays competition from other branded pharmaceutical companies. It goes and it starts the incentives to innovate, because firms know that other firms can use the abuse of the regulatory process to delay entry.

Finally, transparency is the enemy of all this

abuse. The greater disclosure -- going and holding a hearing like this, going and disclosing what individual firms are doing, making information available -- is critical. It's not only so erstwhile academics like Mike Carrier and other people who testified this morning have that information to better inform you. It also is because besides the Federal Trade Commission we have private Attorneys General. We have state Attorneys General, and we have private litigants who can bring cases. And the more information that is publicly available about the abuse of the regulatory system -- things like abuse of citizen petitions, sham product hopping -- the more likely it is that other entities that have rights will be able to go after those problems.

And I wanted to give an example of how to solve these problems by looking at the pay for delay issue. First, there shouldn't be a -- anybody who wants to spend endless hours talking to me, I'll explain that the problem with pay for delay is not an antitrust problem. It's a regulatory problem. As that guy who talks a million times faster than me, from

Apotex, tried to explain, the incentives are all screwed up. The firm that's willing to litigate and then wins -- wins, that's an interesting concept -- wins is the firm that should get the patent exclusivity.

But, how was the problem solved? It was a combination of an FTC study, their power under Section 6 of the FTC Act, where they have subpoena power to ask the companies the questions you can't ask. To go and see their actual internal documents that tell you why they hop and switch, that tell you why they go and adopt a new REMS strategy, that tell you why they, you know, engage in this variety of conduct. They then informed Congress, and then Congress provided transparency in reporting. So, that every patent settlement has to be filed with the FTC.

And when you know that your potentially bad acts have to be filed with the FTC, that does affect your conduct, as the FTC studies have shown that the problematic patent settlements have decreased once people knew that they had to walk before Markus Meier and say here's the settlement, is this settlement

kosher.

Now, let me turn to -- so, let me turn to the three problems. First of all, I have some degree of common sense, even though my wife will disagree. And after hearing David Mitchell's presentation on REMS, I don't think there's another word that you need to hear. David Mitchell's presentation, combined with Mike Carrier's presentation, give you a clear roadmap of what an egregious public problem that is being abused by the branded pharmaceutical industry that has a relatively clear solution, combinations of both regulatory and legislative actions.

Now, in citizen petition, you'd have to live under a stone to think that there was something worthwhile about a process in which people filing these petitions -- oftentimes at the last moment -- only get it right like 8 percent of the time. You can't play baseball if your batting average is 8 percent. And I think the ideas that Mike Carrier has come up with are sound. Let's have greater disclosure of those citizen petitions -- I mean, as much public disclosure as possible. That's what affects the branded companies'

incentives, knowing people will look at it.

Then finally, as to product hopping, I can see why this is a really significant concern. And look, the -- there is a small set of situations where firms really push the envelope. And as long as you can do this in secret, why not? What's the worst thing that's going to happen -- you're going to get involved in ten years of antitrust litigation. But some of these switches are just beyond the pale -- turning a capsule into a tablet, drawing a line across a tablet. I mean, they are just not serious innovations.

Perhaps the FDA should have an obligation -- you know, when you do regulations you have a paperwork reduction act statement in which you have to say that you're not creating unnecessary paperwork. Maybe when you list drugs in the Orange Book, you should have a competition statement, that says that competition will not be harmed by listing these patents in the Orange Book. Maybe you should have to do some kind of broader assessment of the overall impact of extending exclusivity. As the speaker for Public Citizen so aptly put it, the use of exclusivity here is really

egregious and can cause tremendous competitive problems.

Those -- in our written comments, the consumer groups will give you more detailed, more thoughtful comments on specific reform measures. But, I appreciate your questions. Okay. Thanks.

MR. FLANAGAN: Wait, no. I'm sorry. I'm sorry. Questions?

MS. SIPES: Yeah. I'm sorry. One quick question. When you talked about this idea of maybe listing in the Orange Book being conditioned on the listing not having a negative impact on competition, I was wondering if you could say a little bit more about how you felt that determination might be made. You know, obviously, there's the question of trying to make a determination about whether the change itself or the -- you know, if it's a formulation change or something like that, is significant or not. But, I'm wondering if you have any other thoughts to offer right now on how an agency might make that determination.

MR. BALTO: I think it would be great for everybody at the FDA to receive competition training.

I think some kind of analysis of what the impact would be on the market, and how valuable it would be. Look, I don't think you necessarily have to get the answer right. I think you have to ask the question. And once branded pharmaceutical companies know that the question is being asked, just as they know that now when they engage in patent settlements, the FTC may ask the question -- just by knowing that the question gets asked, that will affect their conduct.

MR. FLANAGAN: So, I'm sorry. Is it lawful for us to subject, you know, reformulations to a competitiveness filter?

MR. BALTO: I don't know why you -- that will be a question we will answer thoughtfully when we submit written comments. Thanks.

MS. DICKINSON: Can I ask -- so, full disclosure, the cartoon you have on page 35 --

MR. BALTO: Yes.

MS. DICKINSON: -- I have it on my wall, having worked in Hatch-Waxman for a long time. It's dated 2002. That's 15 years ago. Have -- is it the case that there are actually more incidents of the kind

of product hopping and successive iterations of product development? Or is it that we're feeling we -- the U.S. population feeling the effect of that more, because of the increase in drug prices?

MR. BALTO: I don't know that someone studied the number of things. By the way, I do think if anybody -- if -- I think that the problem in REMS is clearly increasing. On hopping, they are some of the larger drugs and some of the conduct is pretty egregious. But, I don't know that that's been studied. Thanks.

MS. SIPES: Sorry. I'm sorry.

MR. BALTO: Sorry.

MS. SIPES: You're walking faster than we're thinking. I was intrigued by your comment when we were -- in response to my previous question about, you know, a statement about impact on competition where you said that just asking the question has an impact on behavior. Do you -- what do you think of -- you know, you had sort of proposed a statement having to be made or determination about impact on competition. Do you think similar purposes would be served by something

slightly lesser -- for example, simply just increasing transparency around the exact relisting determination that was being requested, or the product that was going to be listed -- simply making that more public in different ways. Do you think that that would -- just putting that information out there would have an effect?

MR. BALTO: I do. I mean, secrecy is the friend of cartelists and monopolists. You know, if they know their conduct isn't going to be looked at and isn't going to be disclosed, they're more willing to engage in that type of conduct.

MR. FLANAGAN: Thank you.

MR. BALTO: Thanks.

MR. FEMIA: Good afternoon. My name is Bob Femia. I'm Senior Vice President of Chemical Medicines at USP. Drs. Gottlieb, Woodcock and esteemed panelists from FDA and FTC, on behalf of USP I'd like to thank the agency for the opportunity to comment on this important topic of facilitating increased competition in the market for prescription drugs through the approval of generic medicines. As we know for more

than three decades, generic medicines have significantly increased patient access to quality treatment while lowering healthcare costs in the United States. We've certainly heard this many times today.

We believe that generic medicines continue to hold similar promise for the future, and we applaud FDA's efforts to modernize and enhance the abbreviated new drug application process, which was created by Hatch-Waxman Amendments, and help ensure the intended balance between encouraging innovation in drug development and accelerating the availability to the public of lower cost alternatives to originator drugs.

USP is an independent scientific nonprofit organization which is dedicated to protecting and improving public health. We collaborate with FDA, clinicians, other practitioners, manufacturers, and many other stakeholders to develop public standards and related programs that help ensure the quality, safety and benefit of medicines, as well as foods. USP shares FDA's goal of advancing and promoting patient safety across medicines, and we support efforts to broaden access to safe and effective generic medicines. Better

access to generic medicines will facilitate the availability of lifesaving therapies, while helping to ensure costs to patients and the healthcare system remain affordable and sustainable, thus upholding FDA's standard for evidence based, science based regulation.

USP offers the following comments for the agency's consideration, and we welcome opportunities to work with the agency, industry and other stakeholders to enhance patient access to quality medicines.

My comments are focused on three main topics. Number one, USP's public standards help facilitate the entry of products from multiple manufacturers to the market. USP's public standards provide common benchmarks which help define the target for quality medicines for industry, also contributing to practitioner and patient confidence in the integrity of these products. In particular, generic drug manufacturers use USP standards to establish the key quality attributes of their products. In this way, USP's public standards facilitate the entry of products from multiple manufacturers because manufacturers can use USP's public standards in their applications to set

forth the quality, purity and strength of their products or substances, thereby minimizing the necessity to establish these parameters themselves, and advancing the availability of lower cost beneficial medicines for patients.

Public standards help both industry and regulators navigate the complicated analytical environment for products. Consider, for example, the category of products frequently referred to as nonbiologic complex drugs. Applications for generic versions of these drugs have presented challenges to industry and the agency. USP can contribute and has been contributing in a positive way to the development of generic versions of these drugs, and in certain cases USP has been able to bring together scientific experts from the manufacturers and the agency to work collaboratively on these challenges.

Through such efforts, common analytical solutions have been identified and agreed upon by manufacturers, and these have led to public standards developments that define critical product quality attributes. It's our understanding that these public

standards in turn have been useful to FDA in its approval of certain nonbiologic complex drugs.

Moreover, USP standards setting process is iterative to account for changes in innovation. USP's product specific standards are flexible to evolve with the public health needs and advances in quality expectations. UPS's standards are reflective of the approved medicine in the marketplace, and evolve as the quality specification for the product evolves. One example is USP's monograph for the drug enoxaparin sodium. This monograph has been revised several times to accommodate subsequent U.S. market entries from different manufacturers for this product.

The resolution of these complex scientific issues is challenging, and requires participation by all impacted stakeholders. Early sustained and active engagement by relevant stakeholders in the standards setting process is imperative for the efficient and successful development of a public standard. USP welcomes the opportunity to work with the agency and industry to explore mechanisms to facilitate this work.

Number two, USP's standard setting process

supports the overall efficiency of the generic drug approval process. USP's processes are built to adapt and respond to stakeholder needs. For example, working closely with the agency and industry, USP created the USP pending monograph process to allow for the development of monographs or monograph revisions for drugs awaiting approval by FDA, to help ensure that the approval of the drug by FDA would be in lockstep with the appearance of the new monograph in the compendia. This new process helps prevent delays in certain drug approvals by reconciling the timing of FDA generic approvals with USP monograph updates.

And third, and last but not least, USP stands ready to collaborate even more effectively with FDA and industry to expand access to affordable quality generic medicines. In addition to this very important public meeting, FDA recently announced other policy initiatives designed to enhance patient access to generic medicines. In order to bring generic medicines to the patients who need them, USP is committed to collaborating effectively with FDA and all relevant stakeholders bringing to the table our scientific

standards setting process and the great responsibility imparted by our statutory recognition for quality standards.

Again, thank you very much for the opportunity to share our comments with you.

DR. UHL: Thank you very much for your comments. Related to the aspect of standards, I'm wondering if you could reflect a bit on the specific example you gave, especially enoxaparin and how the monograph had been updated several times. It sounds to me you could analogize that, potentially, to the earlier comments we received about changes in bioequivalence standards and such, and how you might make recommendations to the agency about how we apply evolving standards with the example of enoxaparin. If you don't have anything you want to say off the top of your head, right now, it might be beneficial to hear about that in the docket.

MR. FEMIA: Actually, the response to that would be best addressed through the dockets. But, as a predicate statement what I can say is that the -- you know, any and all of these issues kind of start and end

with timeliness of commentary to that which appears in the pharmacopeia form. We get requests for revision all the time, for any of our monographs -- any and all of them. When they appear in the PF, we actively encourage and -- to that point, we have a very active program within USP now for stimulating donor participation. Is we really need to have timely feedback from any and all stakeholders -- FDA, any other relevant parties that have interest in that particular monograph need to comment in a very timely manner for PF publications. That's really the cornerstone for any of these evolving monographs, to reflect what's going on in the industry from a regulatory perspective and from an innovative perspective.

MR. FLANAGAN: Thank you.

MR. FEMIA: Thank you.

MS. WORTHY: Good afternoon. I'm Stacey Worthy, the Executive Director of the Alliance for the Adoption of Innovations in Medicine, or Aimed Alliance. We're a nonprofit that works to improve access to healthcare, and thank you for the opportunity to

provide this public comment. Aimed Alliance supports regulatory policies that accelerate both the development of and access to medical treatments. Guarding patient safety and increasing generic drug development are not mutually exclusive, including when it comes to REMS.

First, we recommend supporting efforts to help stakeholders understand the purpose and use of the REMS program. The program limits restrictions only to the most potentially dangerous drugs. For example, the FDA has removed REMS requirements it deems no longer necessary for over 145 drugs already. It also required stricter REMS for certain medications when post-market data showed that these treatments had a known or potential serious side effect not previously understood. Currently, the FDA requires REMS restrictions for 70 medications. Of these, 34 individual medications are regulated with elements to assure safe use, or ETASU, the most restrictive type of REMS. Additionally, there are eight drug classes with REMS where both brand and generic versions use a shared distribution system.

Yet, allegations persist that REMS safeguards, and especially ETASU with restricted distribution, are overused or are implemented by brand manufacturers to block generic competition. Additionally, REMS has become a convenient target for critics who associate FDA mandated restricted distribution programs with the tactics of some industry bad actors that self-imposed restricted distribution to maximize their profits. To avoid misperceptions, the FDA should support efforts to share information on the purpose and use of the REMS program with stakeholders, including policymakers.

Second, generic drug developers must be held to the same safety standards as brand manufacturers, to ensure that patients have more affordable, safe access to higher risk treatments. The purpose of REMS is to first provide treatment options to patients who may otherwise go untreated, and second prevent the dangerous complications these drugs can cause, including severe birth defects and death. Currently, millions of Americans benefit from medications that may have been otherwise unavailable if not for REMS safety protocols. As such, responsible regulatory policy must

ensure that generic drug developers are held to the same safety requirements as innovator companies when conducting bioequivalence testing and marketing their products.

Third, the FDA should provide guidance on negotiating the sharing of samples for bioequivalence testing. In December 2014, the FDA issued draft guidance explaining how generic manufacturers can obtain samples for REMS drugs with ETASU. It allowed brand and generic drug makers to negotiate the sale of drug samples subject to REMS with ETASU, without fear that the innovator REMS program would be violated. However, it only required generic drug makers to attest to the FDA that they were capable of meeting the same safety requirements as the brand manufacturer. Disagreement over this capability has led to stalled negotiations. To prevent such stalemates, the FDA could provide additional guidance on the terms under which the sharing of drug samples for bioequivalence testing can be negotiated. Such guidance could include standardizing the procedures and controls for safe handling and use of high risk drugs, specifying the

quantitative measures to evaluate and validate the REMS programs and methods for filing this information with the FDA.

Finally, the FDA should expand the use of the shared REMS system. Shared REMS systems are appropriate when several generic versions of a medication require the same ETASU program. Shared REMS can use a single web portal, for example, to access medication guides, prescribing information and prescriber and pharmacist education platforms. Presently, negotiating each party's responsibilities in implementing a shared REMS system can take a long time. Challenges include agreement on governance and cost-sharing. One possible solution is creating more industry working groups, to develop proposals for the shared REMS system where FDA acts as a facilitator to resolve problems.

In sum, the REMS program is an essential tool for advancing patient safety, protecting public health and providing access to lifesaving medications that would otherwise not be available. Therefore, we urge the FDA to balance the need for safe use of potentially

dangerous medicines with the importance of increasing the availability of low cost generic drugs. Most importantly, generic drug developers must be held to the same safety standards as brand manufacturers.

Our recommendations are laid out more thoroughly in the comment we submitted to the docket. Thank you.

MR. FLANAGAN: No questions? This concludes today's presentations. Thank you to all our presenters for sharing your insightful thoughts on ensuring a balance between innovation and access. We will take your comments in addition to the comments submitted to the docket under careful consideration. Thank you very much to everyone who attended today, and to others who were watching remotely. Thank you to Martha Nguyen, Ashley Jones, Trang Tran, Derek Griffing and Phil Bonforte who put together this -- and Tawni Schwemer, who put together this terrific event.

Again, the docket will remain open until September 18th. The federal register notice announcing this meeting has instructions for how to submit electronic comments. We'll consider these electronic

comments along with the views presented here today. We recognize your passion for the critical issues that were discussed today, and we're impressed by the willingness of so many of you to share your thinking on complex Hatch-Waxman issues. It will take us some time to digest all of the input we have received, and we'll continue to receive until September 18th. But I can assure you that we have been listening carefully, and we'll leverage your insights to identify solutions where possible.

Thank you again for joining us today. This meeting is adjourned.

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I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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July 31, 2017

DATE JANE W. GILLIAM

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