Public Meeting on Reauthorization of the Generic Drug User Fee Amendments of 2017 (GDUFA)

July 21, 2020

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FOOD AND DRUG ADMINISTRATION

Public Meeting on Reauthorization of the
Generic Drug User Fee Amendments of 2017 (GDUFA)

Virtual Meeting

Tuesday, July 21, 2020
9:01 a.m. to 2:29 p.m.

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Meeting Roster

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PROCEEDINGS

(9:01 a.m.)

MS. NGUYEN: Good morning, everyone. My name is Martha Nguyen, and I am the director of the Division of Policy Development in the Office of Generic Drugs, and I will serve as the moderator for today's meeting.

On behalf of the generic drug program, welcome and thank you for participating in today's virtual public meeting on the Reauthorization of the Generic Drug User Fee Amendment of 2017 or GDUFA. Before I introduce my office director Sally Choe, I wanted to give you a brief overview of today's agenda.

You'll hear from FDA officials, including Commissioner Hahn, and the directors of the Office of Generic Drugs and the Office of Pharmaceutical Quality, Sally Choe and Mike Kopcha, consecutively; then Mike will introduce the panel of FDA experts at today's meeting. After each group of presentations, the FDA panel will have an opportunity to ask clarifying questions.

Next, Maryll Toufanian, the director of the Office of Generic Drug Policy in OGD, will provide an overview of GDUFA II, followed by Elizabeth Miller, the assistant commissioner for Medical Products and Tobacco Operations, who will discuss the future of inspection.

After Elizabeth's presentation, Ashley Boam, the director of the Office of Policy for Pharmaceutical Quality, will present on the future of pharmaceutical quality. After Ashley's presentation, we'll take a short break and reconvene at 11a.m. for a presentation on Complex Generic Activity by Rob Lionberger, the director of the Office of Research and Standards in OGD.

The rest of the morning will be dedicated to presentations from other federal agencies and trade associations. We will break for lunch and reconvene at 1:00 p.m. for presentations from healthcare providers and other stakeholders and an open public comment period. If you would like to speak during the open public comment period, please send a request through the technical support

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chatbox before the lunch break. Finally, Jacqueline Corrigan-Curay, the director of the Office of Medical Policy in CDER, will make closing remarks and adjourn the public meeting.

Again, thank you for your participation in today's virtual public meeting. If you should experience technical difficulties during this event, close the Adobe Connect window and rejoin the meeting or try rejoining the meeting using a different web browser. If this does not work, contact our technical support through this email address, virtual-w0cc-support@fda.hhs.gov.

With that, I will turn it over to Sally Choe to introduce Dr. Hahn.

DR. CHOE: Thank you, Martha.

I'm delighted to introduce Dr. Stephen M. Hahn, who was sworn in as the 24th commissioner of Food and Drugs on December 17, 2019. Dr. Hahn is a dedicated clinician having trained in both medical oncology and radiation oncology. In his previous leadership roles, he has always carefully balanced executive management with the clinical time to

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continue to serve oncology patients, his true passion.

Prior to joining the FDA, Dr. Hahn served as a chief medical executive at the University of Texas MD Anderson Cancer Center, a facility that cares for more than 140,000 patients a year. Before joining MD Anderson, he served as the chair of the Radiation Oncology Department at the University of Pennsylvania's Perelman School of Medicine from 2005 to 2014.

Dr. Hahn earned the rank of commander in the U.S. Public Health Service Commissioned Corps while at the National Institute of Health, National Cancer Institute, where he also completed a fellowship in medical oncology and a residency in radiation oncology. He also completed a residency in Internal Medicine at University of California, San Francisco. Please join me in welcoming. Dr. Stephen Hahn.

Presentation - Stephen Hahn

DR. HAHN: Thank you, Sally, for that introduction.

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I want to welcome everyone today to the public meeting on GDUFA. The public meeting process is an essential element of the FDA's commitment to public health. Our ability to faithfully fulfill our mission to protect and promote the health of the American public and to build on our successes to meet the future public health needs of the American public relies in great part on our knowledge and understanding of hearing from the public.

Meetings like this one, designed specifically for us to have the opportunity to hear from a broad range of stakeholders, are vital to that process. Looking over today's agenda, I'm pleased to see that we have a full representation of these groups from patients and consumers to healthcare professionals, scientists, and members of industry.

Perhaps no area of FDA's vast set of responsibilities is this accessibility and transparency more important than in the role we play in helping to expand access to affordable

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medications. Ensuring that patients who need safe and effective medicines and have greater access to them is a public health priority for us. It is central to the work of the FDA, and it has also been a key element of my work throughout my career.

We know that competition from generic drugs can help lower drug prices and improve access for American patients and consumers. Three years ago, when we launched the FDA's Drug Competition Action Plan, DCAP, one of our priorities was to improve the efficiency of the generic drug development assessment and approval process. We've made enormous strides with this plan, which is completely consistent with and builds on the commitments and goals reflected in the GDUFA II agreement.

As a result, we brought greater predictability and timeliness to our assessment of generic drug applications while increasing access to safe, high-quality, and more affordable generic drugs, all the time always maintaining our rigorous approval standards.

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These efforts are even more critical today as we are immersed in the consuming effort to find treatments and cures in response to the COVID-19 pandemic. Even as our agency is working full steam on our COVID-19 response, we continue to focus on our critical role to ensure access to lower cost, safeand effective high-quality generic medicines. Across the FDA, many of our staff continue to focus on these and other mission-critical initiatives, and I am so incredibly proud of the more than 17,000 FDA employees during this time.

I especially want to recognize the Generic Drug Assessment Program team for its work in ensuring that the program has continued with minimal interruptions during this time. During this public health emergency, the FDA has prioritized the assessment of generic drug submissions for potential treatments and supportive therapies for patients with COVID-19.

We've approved a number of important generic drugs for this purpose, including some used mainly in intensive care unit settings for patients

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requiring mechanical ventilations and others that have seen increased demand. Throughout, we've maintained FDA's gold standards of evaluating products based on quality data and sound science.

The FDA has also been working with generic drug applicants whose development work has been affected by the COVID-19 pandemic, and we've also worked diligently to support manufacturers of approved generic drug products who need to make changes to a manufacturing process or facility to address disruptions from the COVID-19 pandemic.

We significantly expedited the assessment of these types of changes, known as supplements, to approve generic drug applications. Indeed since February, our generic drug program has worked with companies to approve close to 300 of these ANDA changes, which have helped maintain the supply of medications for our most critically ill patients with COVID-19, including antibiotics, sedatives used in ventilated patients, anticoagulants, and pulmonary medications. And really, this is a partnership with the industry and many of you here

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that we are able to do this and very much appreciate that collaboration.

Now, even as we respond to COVID-19, we have continued to work to ensure access to safe and effective generic medicines beyond those needed to respond to this immediate crisis. The generic drug program itself is stronger than ever before, and we continue to take actions on COVID-19 and non-COVID-19 related ANDAs.

Even during this pandemic, we are on target to meet our GDUFA goal of assessing and taking timely action on at least 90 percent of original generic drug applications, as we have since 2015. In the first six months of 2020, FDA approved, or tentatively approved, 361 ANDAs, including 35 first generics, but the impact of GDUFA funding on American patients goes beyond approval numbers.

GDUFA regulatory science research provides needed information and tools for industry to develop new generic drug products. It allows us to make recommendations that support appropriate science-based methodologies and evidence for the

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development of generic drugs. In combination with the implementation of DCAP, GDUFA is helping make approval of generic drugs easier to obtain by proactively addressing scientific and regulatory challenges that may arise.

With GDUFA I and II, the FDA has demonstrated its leadership in helping to ensure that more safe, effective, high-quality generics are available to patients who need them most. With each authorization of GDUFA, the program continues to improve predictability and transparency, driving an efficient and effective application assessment process.

Of course, we know that there's much work to be done, and part of today's event is to actually receive as much feedback as possible and have a bi-directional conversation, and we look very much forward to that.

Thanks to the hard work and the collaboration of industry and the FDA, we've built a modern generic drug assessment program with the necessary IT capabilities and the scientific and

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operational sophistication that came into being under GDUFA. As a result, the United States has a very strong pipeline of generic drug applications and a robust development pathway.

We will not rest on past successes. We are a learning organization and want to get better. We will apply the same energy, resourcefulness, and innovation we are currently demonstrating in our efforts to defeat COVID-19 to further increasing accessibility of all medications for the benefits of patients and consumers.

We look forward to hearing from all of you as we develop GDUFA III and work to strengthen the generic drugs program in ways that will even further enhance public health. Thank you and have a great meeting.

MS. NGUYEN: Commissioner Hahn, thank you for your remarks, for your leadership, and steadfast support of the generic drug program, especially during these challenging times.

I now invite Sally Choe, the director of the Office of Generic Drugs, to provide her remarks.

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Presentation - Sally Choe

DR. CHOE: Thank you. It's my pleasure to welcome everybody once again and to give these opening remarks along with my colleague Dr. Kopcha following Dr. Hahn. We introduced the reauthorization process building from the success of GDUFA I and GDUFA II, which enables the most robust generic drug review program to date.

The continued work between FDA and the generic pharmaceutical industry's GDUFA III program will ensure that Americans will continue to have access to safe, high-quality, and more affordable generic drugs.

Dr. Hahn has already noted how important generic drugs are in helping lower drug prices and improve access for American patients and consumers. I would like to mention briefly the particular role generic drugs play in the current public health emergency by providing access to drugs facing increased demand and in short supply and drugs vital to the care of patients suffering from COVID-19, such as those used in ICU settings for

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patients requiring mechanical ventilation.

I won't go through this whole list, and it's not even an exhaustive list of all of the generic drug approvals used in the COVID-19 response over the past three months. However, I wanted to show this example to demonstrate how FDA prioritizes the assessment of generic submissions in support for patients with COVID-19, which is all possible because of the enhanced generic drug program and its improved flexibility due to GDUFA, allowing us to prioritize assessment of generic drug submissions and involving the supportive therapy for patients with COVID-19 while still maintaining the rest of our usual work.

This really shows the result of our successful GDUFA program, and you will enjoy hearing the specifics from various speakers from the agency, starting with my colleague, Dr. Kopcha, in his opening remarks, and then Ms. Maryll Toufanian, and others today.

Now to quote our usual GDUFA work, there have been various commitments that have been worked

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out between the agency and the industry, and let me start from the communication side. Mutual commitments to the assessment process has shown clear value, and more clear communication from FDA and complete timely response from applicants significantly enhance the process.

Building on the success of GDUFA I, GDUFA II included increased communication and collaboration with the industry, provided additional support to applicants preparing their generic drug application, and streamlined the business process to increase first-cycle approvals and worked to get faster approvals.

To improve the predictability, transparency, and efficiency of the review process, as well as to minimize the number of review cycles leading to approval, FDA agreed in GDUFA II to issue communications related to ANDA efficiency duringthe course of the review of original ANDAs.

FDA continues to embrace these mechanisms and communicate extensively with industry. These mechanisms include information requests, IRs;

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discipline review letters, DRLs; and complete response letters, CRLs. These requests and letters detail important issues that need to be addressed by applicants before FDA can approve an application.

Another important tool I'd like to mention is controlled correspondences. A controlled correspondence inquiry is submitted to the agency by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of a generic drug product development.

The staff that responds to controlled correspondence is the same assessment staff that is part of the assessment process. The opportunity for industry to submit controlled correspondence supports the development and submission of a higher quality generic drug application.

FDA's effort to increase the review efficiency and thereby improve patient access to generic drugs also has been greatly enhanced by the agency, making regulatory and scientific policies

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available to applicants and the general public. This includes guidances for industry where FDA publishes to share the agency's current thinking and recommendations to industry and specific topics covering generic drug development, pharmaceutical quality, regulatory review, and the approval processes, with many more.

Product-specific guidances, PSGs, provide the agency's current thinking and expectations on how to develop generic drugs that are therapeutically equivalent to specific brand name, reference-listed drugs. PSGs also help applicants submit ANDAs with efficiency, which can lead to more first-cycle approvals.

PSGs are intended to make industry's research and development decisions more efficient and cost effective by identifying the most appropriate methodology and evidence needed to support a specific generic drug's approval, and of course the manuals of our policies and procedures, MAPPs, describes internal agency policy and procedures and are accessible to the public to help

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make the agency's operation more transparent.

FDA also engages in outreach efforts to inform industry participants and other stakeholders about GDUFA II and the generic drugs program. Some examples of annual meetings we have hosted this year are our 2020 Generic Drug Forum, which took place in April, helping applicants achieve success and minimize common deficiencies in the development of generic drug applications.

Also in May, in the GDUFA Generic Drug Regulatory Science Initiative Public Workshop, we solicited input from the public, industry, and academia to develop an annual list of science and research priorities for generic drugs, which support PSG development, ANDA submission assessment, and the pre-ANDA program. Both meetings were successfully conducted 100 percent virtually.

This coming September, we have the Advancing Innovative Science in Generic DrugDevelopment Workshop, formerly known as the Complex Generic Drug Development Workshop, intended to help the

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generic industry, scientists, researchers, and regulatory affairs professionals pave a clear scientific pathway for generic drug development by focusing on common scientific issues and deficiencies in ANDAs.

We also hold events based on timely issues, such as another upcoming workshop on the Orange Book, which will celebrate its 40th anniversary this year. In addition, we have experts from FDA present at various webinars and conferences and published articles. And lastly, here I have listed some of the use of websites that give tons of information on generic drug programs, which can be easily accessed by all of you.

While the recent public health emergency has reminded us of the importance of being prepared for whatever the future may bring, thankfully GDUFA I and II already had FDA's generic drug program working in a forward-thinking manner. The GDUFA program is strategically designed to support the development of generic drugs long before the submission of applications. It has helped in

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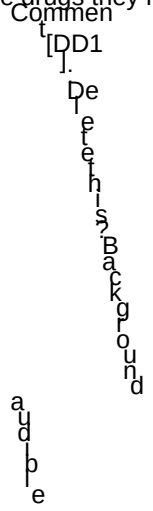
accessing, that generic drugs can be available to patients as soon as patents or exclusivities permit application approval.

The GDUFA-funded Science and Research Program and the Pre-ANDA program are two such examples of FDA's strategic, proactive approach to supporting generic drug development and assessment.

First, GDUFA regulatory science research provides needed information and tools for industry to develop new generic drug products. It enables us to make recommendations that support appropriate science-based methodology and evidence for the development of generic drugs. This type of work is particularly important for complex generic drug products, which are harder to genericize and often have less market competition.

We directly support developers of complex generic drug products to ensure that patients and consumers have access to the drugs they need at



prices they can better afford.

Here are some of the examples of approvals of complex generic drugs, where GDUFA-funded

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research directly facilitated the assessment and approval during GDUFA II. Albuterol sulfate inhalation aerosol, fluticasone propionate/salmeterol inhalation powder, and acyclovir cream are just a few examples.

The Pre-ANDA program established under GDUFA II, the Pre-Abbreviated New Drug Application program, provides product development assistance to generic developers through written communications and meetings with industry to help clarify regulatory expectations early in the generic drug development process and during FDA application assessments.

This program provides a special focus on complex generic products such as some inhaled or injectable products, which are usually harder for generic drug developers to develop, often leading to a lack of generic competition even after patents and exclusivities no longer block general generic approval.

I think this is my last slide. This is a photo of the Office of Generic Drug's summer picnic

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from last year, 2019, which I have been displaying in various meetings.

Why? I want to remind us that despite today's pandemic challenge, which forces us to have a virtual presence in so many important events like today's public meeting, we have incredibly dedicated individuals not just from the Office of Generic Drugs but in the Office of Pharmaceutical Quality and many other offices across the center and agency, working hard continuously in the generic drug program. I know the same goes to industry, academia, and all of the organizations that you represent.

With GDUFA I and II, FDA has demonstrated leadership in helping to ensure that more safe, effective, high-quality generics are available to the patients who need them most. We have established a generic drug program that is strategically structured in activities and communications with industry. With each authorization of GDUFA, the program continues to improve predictability and transparency, driving an

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efficient and effective application assessment process. As a result, the U.S. has a very strong pipeline of generic drug applications and a robust development pathway.

Once again, all of this is possible as a result of the hard work industry and FDA have engaged in building a more modern generic drug assessment program. I hope you enjoy the rest of today's virtual public meeting, and we look forward to working with you. Thank you.

MS. NGUYEN: Thank you, Sally.

Now I invite Mike Kopcha to provide his remarks. Mike Kopcha is the director of the Office of Pharmaceutical Quality.

Mike, after your presentation, please introduce the panel of FDA experts at today's meeting. Thank you.

Presentation - Michael Kopcha

DR. KOPCHA: Thanks, Martha. I appreciate that. And thank you, Dr. Choe, for the introduction as well.

As Sally pointed out, OPQ, the Office of

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Pharmaceutical Quality, is one of the many offices that support the generics program, so I'm glad to be part of that group and part of the work that's done to bring generics to the marketplace.

The topic for my presentation today, GDUFA and Pharmaceutical Quality at FDA, are programs that have grown up together. The reason why I entitled it that is because when I joined the FDA back in November of 2015, the GDUFA II negotiations were just starting up, so I was able to get introduced into the programs, not only GDUFA but PDUFA as well.

So I do feel alliance with the UFA programs, and now that we're going through the reauthorization, I'm kind of growing up now, going into the third iteration for GDUFA itself.

Let me go on to the topics I'm going to be presenting today: a life cycle approach to pharmaceutical quality and give you a little bit of background on that; FDA's research and how that informs quality assessment; innovations in FDA's generic drug assessment; and generics in the time

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of COVID-19.

Let me start out with the life cycle approach to pharmaceutical quality. What I typically like to do is kind of ground people in terms of quality itself, and pharmaceutical quality more specifically. A quality product of any kind consistently meets the expectations of the users.

People feel real comfortable talking about quality when it comes to things like computers, automobiles, smartphones, but I do want to communicate and share with you that drugs are no different. They need to consistently meet the expectations of the end user, and for us that end user is both patients and consumers.

Patients expect safe and effective medicines with every dose that they take, and the way I like to define it is that quality ensures the safety and efficacy of the next dose; which makes it just an easier way for me to explain pharmaceutical quality. Pharmaceutical quality is what gives patients confidence in their next dose of medicine, as I mentioned.

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Now what I'd like to do is to get into the quality over the drug product life cycle. One of the hallmarks of CDER's quality program is the focus that spans the entire drug product life cycle, my Office of Pharmaceutical Quality. This means we are involved in the quality of a product from the time it is born as an IND, or an investigational new drug, to the time that multiple generic competitors are approved and brought to the market.

This approach emphasizes knowledge sharing across the life cycle, which is a key thing for us and it's essential for quality oversight. It enables us then to ensure quality medicines are consistently available to patients and consumers. It enables us then to proactively prevent drug shortages. Very importantly, it enables us to ensure parity between brand and generic products.

We've seen successes of this life cycle approach play out under GDUFA. One example is ensuring that innovator drug labeling is current and complete such that it enables the development

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and eventual approval of more generic drugs. Inaccurate innovator labels would then, of course, limit generic competition.

Another example is the integrated quality assessment, which is a team-based approach or team-based process that brings quality discipline experts together to solve difficult issues. This team-based approach has led to the approval of many difficult critical generic products under GDUFA.

What I'd like to do now is to transition over to FDA research and how that informs the quality assessment, but keep in mind that if we wait to address the underlying science of generic drug applications until they arrive on the doorstep, then it's already too late for us. So we need to do that proactively and we need to do that in advance of these generic products coming into the center.

For this reason, we've built a strong proactive science and research program under GDUFA. With this proactive approach to science and research, we can be prepared then to respond. For

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example, this may prepare us to address consumer complaints or face public health issues.

It is also very forward-looking, as we want to make sure we're prepared to handle the latest technologies and process control and advanced manufacturing, the latest in advanced analytics, and the latest advances in drug design and formulation. After all, with our life cycle approach, new drugs are already viewed as the future generic drugs. That's kind of how we view it within the program itself.

Let me explain to you or give you a little bit of an idea what I mean by advanced manufacturing. This is one of the areas that I typically like to talk about because it's extremely important across all the programs, all the UFA programs that we're dealing with.

In terms of what's novel manufacturing, most people would say, "Well, novel manufacturing looks at the methods to improve process robustness in efficiency." But the way we define it, it goes even beyond just the manufacturing methods because

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the manufacturing methods then lead to the dosage form. So novel dosage forms and delivery systems to improve drug delivery and targeting is also defined as part of advanced manufacturing.

Well, now there's a third part because in order to make those dosage forms using advanced manufacturing, you need to be able to analyze them. So the third part then becomes novel analytical tools to improve product quality testing, process monitoring, and/or process control, and that's how we define advanced manufacturing.

So advanced manufacturing is coming in the generics industry. We've seen a lot of interest in this area, and we've also received applications that have come into the program. But let me explain how our research program directly enables generic drug approvals. One example is abuse-deterrent formulations of generic opioid products. These are part of FDA's action plans to address opioid addiction.

Our research fuels the understanding of formulations necessary for the assessment of what

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we call ADF or whatchama-call-its, for the ADF. It's the abuse-deterrent formulations that we have. Also, another example that we use is locally-acting ophthalmic drug products. These ocular drug products then are also particularly important to us for developing and testing bioequivalence to the innovator products. Our research directly contributed to the development of guidances related to these types of products.

What I'd like to do is go on to transition into innovations in FDA's generic drug assessment. It's not enough to simply be prepared for industry's innovations; we also need to make sure that the FDA is being innovative in the way we conduct our business, particularly related to quality assessment.

The future of quality assessments looks like this. It's the knowledge-aided assessment and structure application or what we call KASA. You'll hear more about KASA later on, but briefly it's a database platform that will take structured data from applications and use it for structured quality

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assessments. Importantly, it will assess risk and enable efficient knowledge management about products, process, and facilities across the life cycle, from the IND, all the way through to generic, all the way through to post-marketing activities that need to take place.

We talk about managing the life cycle of a product, and KASA, this knowledge-aided assessment and structured application will allow us to do that more efficiently and more effectively and make use of the learnings across the life cycle. But KASA isn't just the future; it's also the present. We have already used an iteration of KASA internally for some solid oral generic drug product quality assessments.

So as we always like to say, the future is already here. KASA has clear benefits to us at the FDA. It enhances our consistency and objectivity. It enables knowledge management as it relates to sharing information about products, manufacturing, and facilities. It also accelerates our regulatory actions and decision making.

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What I want to point out is that KASA has similar, if not better, benefits for patients and industry as well, which is always our ultimate focus. It should provide for clear regulatory expectation and enhanced transparency and enhanced consistency and application assessment. It also increases the ability for first-cycle approvals, and this is particularly so for generics, but important not only for generics, but for new drugs as well. It should lead to more affordable and accessible medicines, importantly, while making sure we hold the same lofty quality standards.

Transitioning into generics in the time of COVID-19, if KASA is what the future holds, what I'd like to talk about now is how GDUFA is benefiting everyone right now, even in the time of COVID-19. Much of the press is focused on new drug discovery and development, but generics have played a crucial role in our nation's COVID-19 response as well.

The error of COVID has made our job harder, but many of the issues we're dealing with are ones

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we've been bringing to light for years. This includes the complexity of the supply chains that we deal with, drug shortages, and also decisionmaking based on changing science and risk. So COVID-19 has really brought these to the forefronts even though we've known they've existed for a period of time.

You've seen and perhaps benefited from some of the things GDUFA has enabled us to do related to COVID. We've helped secure the supply chain by expediting the quality assessments of hundreds of application supplements, and we've also approved hundreds of these supplements.

We've granted regulatory discretion to accelerate post-approval changes to provide flexibility to manufacturers. For example, based on risk and medical necessity, we've downgraded some prior approval supplements to changes being effected supplements; and where possible, we've been driving COVID-related ANDAs to first-cycle approvals through a combination of information requests and good old-fashioned hard work. Nothing

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ever replaces good old-fashioned hard work.

When I look at who's benefited from GDUFA, that does not exclude us at the FDA as well. Like all of you, we rely on generic medicines as well for our health and well-being, so don't forget that we are patients, too. Let me close then by asking that we continue using GDUFA to give us our confidence in our next dose of generic medicines. I thank you for the time and for allowing me to give my opening remarks.

Introduction of Panel -

- Michael Kopcha

DR. KOPCHA: As Martha had mentioned, what I'd like to do now is to go through and make you aware of the individuals that are going to be our FDA GDUFA III Q&A panel of experts.

I'm going to start with Dr. Jacqueline Corrigan-Curay. She's the director of the Office of Medical Policy at CDER; Mr. Alonza Cruse who's the director of the Office of Pharmaceutical Quality Operations at the Office of Regulatory Affairs; Ms. Ashley Boam who's the director of the Office of Policy for Pharmaceutical Quality at OPQ;

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Ms. Maryll Toufanian who's the director of the Office of Generic Drug Policy at OGD; Mr. Ted Sherwood who's the director of the Office of Regulatory Operations at OGD; and Dr. Robert Lionberger who's the director of the Office of Research and Standards at OGD.

They will actually be with us today, throughout the public meeting today. At certain allocated time points, we will have the panel of FDA experts clarify questions of our external guest speakers to make sure we have a clear understanding of the points and the concerns, or even some of the positive things that outside speakers may have about the program.

Martha, I believe I now turn it back over to you.

MS. NGUYEN: Thank you, Mike. Thank you for your remarks and for introducing our panel of FDA experts.

Next I'd like to introduce Maryll Toufanian, who, as Mike said, is the director of the Office of Generic Drug Policy. She will be providing an

overview of GDUFA II.

Presentation - Maryll Toufanian

MS. TOUFANIAN: Good morning. It's my pleasure to be speaking with you all today. I have the good fortune of being part of the team that is intimately involved in implementing the GDUFA II agreement, and I have the pleasure of doing so because it has been such a tremendous collaborative endeavor with many of the folks who are joining our public meeting today, and more generally within the industry community and the more general public stakeholder community.

To refresh folks' recollection, the GDUFA II agreement really builds on the fundamental restructuring that took place under GDUFA I, which as we all know established the modern generic drug review program under a user-fee paradigm. GDUFA II really streamlined and finessed the GDUFA I agreement, targeting where there could be more improvement in our work with industry to facilitate the availability of generic drug products as soon as possible.

The core of the GDUFA II agreement had two major objectives. The first was reducing the number of review cycles to approval and, two, increasing those approvals to ensure that safe, high-quality, and lower cost generic drugs were available.

Features, which Sally and Mike both described in some detail, included the new pre-ANDA program really focusing on how we can get those more complex generic products that are more difficult to genericize into our queue factor and reviewed more quickly, making sure that we are transparent and proactive in our support of not only the assessment of those products but really the development.

In addition, there were new review goals for priority ANDA submissions, again seeking to facilitate more efficient and timely assessment and approval, greater accountability and reporting, and a slightly modified user-fee structure; again, all with the intent of going from good to great, as we did from GDUFA I to GDUFA II.

GDUFA by the numbers, I think that we are very proud as a generic drug program to have achieved what we did during GDUFA II. As reflected on the slide, we had over 2,000 approvals, over 550 tentative approvals as of mid-point this year, and it's a result of a tremendous effort both by the program, but also our partners in industry in stepping up and engaging all of the important tools and all of the important process improvements that we contemplated as we negotiated the GDUFA II agreement.

But obviously numbers, approval numbers and tentative approvals, are not the full story. So for the next few minutes, I'm going to take the opportunity to go under the numbers or beyond the numbers, and share with this group a little bit more of what goes into a successful generic drug program.

First we have the graph cap [ph] numbers that we talk about when we talk about our assessment and work we do prior to ANDA submission. A complete response letter is what we send to

industry upon assessment of a generic drug application, listing out all of the deficiencies that we've identified need to be resolved. We've worked tirelessly to provide that information to industry, and we're working on making those communications even more efficient, more clear, and more helpful to industry.

Even before we issue the complete response letter, two very important features of GDUFA II is the opportunity that FDA has to communicate deficiencies and ask questions over the course of a review cycle to ensure that we have as much information as we can get in order to evaluate the generic drug submissions. As you can see, the numbers speak for themselves.

Each one of those thousands of communications reflect a significant amount of work by multiple parts of the review assessment program, ensuring that we are, as nimbly and efficiently as possible, identifying next steps for resolution of outstanding scientific and regulatory issues with a particular submission.

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A significant number of drug master file completeness assessments have been done. This is that first step that's necessary for a generic drug applicant to reference a drug master file; again, trying to make sure we're doing that as efficiently as possible so that everything comes together in a way that facilitates a more efficient generic drug assessment.

A significant amount of work has been done prior to ANDA submission by our scientific groups in the form of controlled correspondence, which give folks an ability to ask specific questions, and a really exceptionally successful pre-ANDA program. Those series of meetings, both prior to ANDA submission and during the ANDA assessment, gives a really significant amount of scientific attention to those harder to develop complex generics.

With success, and I'll be talking about this in a little bit more detail later on, comes a very, very important -- and I think Sally and Mike in particular reference that once we approve a

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product, we are totally committed to making sure that product remains a safe, effective, and high-quality product. That involves our continued work reviewing prior approval and was referred to as changes being effective supplements.

These are the opportunities to make sure that the product is both up to date with respect to labeling and quality and really ensuring that the American public has the very best generic drug products that can be made.

In addition to these more formal communications and paper exchanges, I'll note that -- and I think that this is actually an undercount -- there is a significant number of more informal communications between various parts of the review program and applicants, really trying to facilitate that dialogue in a way that makes clear to industry applicants and other industry stakeholders what our scientific and regulatory standards are so that they can meet them.

Now stepping back from the director review work, as Sally alluded to, all of that work is

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really complimented by a second or third circle of work, and that is the work that the offices in the program in general do to make our regulatory and scientific processes, requirements, and recommendations as transparent and clear as possible to industry and public stakeholders.

We've issued in GDUFA II over 27 draft and final guidances with topics across the spectrum, and some are very practical. Here is what we agreed to in GDUFA II and here is how we propose to implement that agreement.

Guidances are a vital way for us not only to provide our ultimate recommendations, but in almost an iterative process, propose our plans for implementation, receive very important feedback from the public, and then finalize those recommendations so we can provide as much transparency as possible.

We issue guidances on a number of scientific topics, including very important communications on how we recommend the development and our evaluation of complex dosage forms; combination products;

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peptide products; abuse deterrence; and consensus standards.

Finally, there are a number of draft and final guidances that provide important recommendations and background for those parts of the program that aren't necessarily front and center when we think about assessment, but yet a vital cog; and that is the work that we all in the generic landscape understand to be very complex with respect to the important incentives embedded in the Hatch-Waxman amendment that established our program over 30 years ago in terms of the incentives for new drugs, the patent and exclusivity provisions of the law, and how those are implemented by the generic drug program recently.

For example, we went beyond what is normally considered part of the nuts and bolts in GDUFA, but really sought -- in both the draft guidance describing the work of the Orange Book, which is the soul of regulatory information for both new and generic drug review -- and in addition asked the

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stakeholders how can this publication and how can our work implementing certain provisions of the statute related to patents and exclusivity be enhanced.

In addition to the guidances, we issued over 20 MAPPs with topics as broad as how we're going to communicate with industry, what you all can expect from us, more transparency on our review assessment activities, and the pre-ANDA process.

All of this work is reflective of a significant amount of collaboration, time, effort, and coordination among all of the people who are also reviewing the generic drug applications, and a significant number of people who you may not think about, including those within the policy programs, those within the Commissioner's office, and those who within the Chief Counsel. So it really does take a village, and some of these efforts show the fruits of those endeavors.

In addition, in the next circle of efforts, we have provided a significant number of informational activities directly supporting

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generic drug access. Sally referenced some of these. I won't go into great detail, but I think it's notable that much of this, again, was not necessary and was not part of our direct commitments under the GDUFA II agreement, and yet we identified the need to go above and beyond and provide, in creative ways, additional information to facilitate the success of the generic drug program.

Those activities included the creation of several informational web pages, and I'll feature two in particular. One was what we refer to as the "Overhaul of the Paragraph IV Certification Webpage." As I referenced previously, there's a significant overlay of intellectual property elements to our regulatory process, one of which is providing information that is essential for industry to plan when first generics likely will be able to be approved as informed by the patent and exclusivity landscape.

We noted that while there was certain information available, we had received feedback

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that it would be much more helpful to provide additional information, so we created that because in addition to making sure that our assessment process is streamlined and as efficient as possible, our implementation of the patent exclusivity provisions of the statute really necessitate and can be facilitated by greater transparency on when a product can actually get approved.

In addition, there were statutory mandates that were contemplated during the GDUFA negotiations that were implemented and we're committed to implementing successfully, including a totally new element of our review program in the competitive generic therapy pathway to incentivize generic competition for older product for which there was limited generic competition, and a webpage on CREATES implementation that helps facilitate a very important part of recent legislation; and that is facilitating the availability of samples for generic developers and conducting their pre-submission evaluative testing.

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This is something that I think we heard loud and clear and Congress ultimately heard loud and clear, was the problem inhibiting generic drug development. We embraced the results of CREATES and provided what we think is very helpful information about how we are going to implement that to facilitate generic drug development.

As Sally described, and I think Rob will detail later, there's been a significant number of webinars, podcasts, and events hosted by the FDA Small Business and Industry Assistance program on a number of topics. The terrific news about this, and much of our work, is that it's available on our website for all to resource and continue to resource, helping both seasoned ANDA applicants but also those new ANDA applicants who we welcome and embrace.

There's extensive individual participation in external regulatory and scientific meetings and a significant number of scientific publications taking that work that I think Rob will discuss in more detail and making that available. In

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addition -- and I know that Ashley will touch on some of this -- there's a significant program, and I would say agency commitment, to the global landscape and the reality that the generic drug work that we all do is actually part of a larger global endeavor. We're committed to maximizing harmonization and in particular our work with the International Council for Harmonisation activities.

There is more on that to come but, again, something that wasn't necessarily contemplated in the GDUFA II agreement and yet really complements those fundamental goals and objectives that we all identified.

The good news is that not only does industry, the generic drug program, and the agency but really the whole government and the administration has been behind and a huge champion -- especially, I'm always impressed with Dr. Hahn because there is such a tremendous amount of work to be done by FDA. Yet, since he stepped on campus, he has been a real champion and very much involved in ensuring that the important

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purposes of GDUFA II and the Drug Competition Action Plan are furthered under his leadership, in addition to the significant CDER and obviously program support.

The Drug Competition Action Plan, as Dr. Hahn referenced, really complements and facilitates an extension of those particular policy efforts that directly support the important work we're doing under GDUFA II.

Three tenets of that is including increasing transparency and efficiency in FDA assessment; enhancing the development of complex product review; and reducing gaming by innovators and other stakeholders that may frustrate or delay generic approval. All of this, again, is that next concentric circle that really is showing the multiple layers of our commitment and our desire to make our GDUFA II agreement successful.

At the end of GDUFA II, where are we? As a result of GDUFA and the efforts that I've detailed, and many, many, many more on the part of the agency and of industry, I think we have all demonstrated

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the ability to do what it takes to meet the goals of the agreement. That just doesn't mean the numbers; it means making sure that all of the work that we do complements and helps us achieve those goals.

We have healthy generic program study numbers of applications with industry and FDA, which is a real indicator of the health of the program. While numbers, submissions, and approvals or action numbers will ebb and flow as the work of the industry and the agency works through, I think we now have really achieved a successful modern, nimble review program. We have the most predictable and transparent assessment process to date and, as Rob will detail, a thriving, strategically positioned science and research program.

So what does all of this give to us? Really, a springboard to GDUFA III, and that's why we're here today, is to set the stage and really invite important public comment on what's in light of the successes. Certainly there have been

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challenges in implementing the GDUFA II agreement. What can we do better?

Looking ahead, I know from the agency's perspective, the next authorization cycle creates new opportunities to further enhance the program and the partnership. Always with success comes responsibility. As I alluded to previously, there has been a significant increase in supplements to approve ANDAs. We embrace those supplements as important to maintaining safe, effective, and quality medicines we all take.

In addition, we have additional safety surveillance responsibilities that we take very seriously. In addition to the work we do to approve the product, we have an entire staff and many, many people in our partner offices within CDER and FDA committed to surveilling the landscape of drugs, including generic drugs, to ensure that if there are signals related to potential safety or efficacy concerns, we are proactive and embrace the tools we have and develop new tools to ensure that products out there we are all taking are safe and

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effective.
I think there's also still work to be done to further enhance the efficiency and transparency of our work and to gain more first-cycle approvals, which benefits not only those folks at the negotiation table, but more importantly those individuals and American patients to get those products as soon as they can.
I think we also realize that we must be forward-thinking. We must anticipate what the future generic drugs submission horizon looks like. I think Rob will describe in more detail as drugs become more innovative when they are first approved by FDA, we have a responsibility in the generic drug program to make sure we are ready to assess and review those products, notwithstanding those complexities, to ensure they are substitutable as they come in as generics.
I think there's an extraordinary amount of rapidly advancing technologies. Mike alluded to many of those in the manufacturing stage, and I think Ashley will to come. But it's not limited to

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manufacturing. I think there's a whole host of really exceptional work coming out of our research activity just in general that a GDUFA program should be able to embrace.
I think all of that requires us to embrace creative thinking. As I like to say, I'm fortunate to work with the smartest people I know. I'm humbled by that work. I'm equally humbled by the work that I see industry and other important public stakeholders bring to the table. In order to really maximize the success of the program, we need to embrace that creative thinking.
In closing, I'll say that we often reflect on what we can do better, what industry can do better, and what stakeholders can do better in making sure there's a return on our investment. For us, and I think all of us in the generic drug community, we understand the most important return on investment is that return we get to see there in public, to the folks who take generic drugs and rely on generic drugs every day.
I'll echo what everyone has said before me,

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that I think although the current global pandemic is profoundly foundationally challenging our nation, I think that we as a collaborative generic endeavor have been able to address some of the deep challenges with respect to access because of the successes of what we've all been describing. Our responsibility now is to make sure that the next authorization allows us to continue to be nimble and embrace any challenges that may come.
With that, I will turn it back over to Martha Nguyen.
MS. NGUYEN: Thanks, Maryll, for your comments.
Next is Elizabeth Miller, the assistant commissioner for Medical Products and Tobacco Operations, who will speak with us about the future of inspections, in particular, the role of the Office of Regulatory Affairs.
Presentation - Elizabeth Miller
MS. MILLER: Hi. Good morning, and thank you so much for inviting me to present. I hope everyone is well and staying safe. It's my

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pleasure to be joining you as I begin my fourth month back at FDA in the Office of Regulatory Affairs. Today I will be sharing ORA's perspectives and information about the future of inspections.
I'd like to frame the discussion with some overarching perspective. Together we have shared goals that include work we do to help ensure that U.S. patients and the U.S. healthcare systems have access to a secure and consistent supply of critical pharmaceuticals. ORA's mission is protecting consumers and enhancing public health by maximizing compliance of FDA-regulated products and minimizing risks associated with those products.
Our mission and the public health outcome, as we strive to achieve, are closely aligned and frequently mutual; and as such, it's critical that we at FDA appropriately partner with regulated industry to realize the intended impact. The diverse and resilient pharmaceutical supply chain is critical to our nation's health, and a reduction in dependence on any one country for key

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pharmaceuticals or their components contributes to our national security. Industry owns the primary responsibility to reliably produce quality, effective, and safe products.

The medical product industries we regulate must adhere to current good manufacturing practice requirements pertaining to, for example, operating procedures, manufacturing, sanitation, and processing controls, and are subject to certain reporting requirements about their facilities. Furthermore, there is expectations that the development of generic product data and the integrity of those data are sound.

A little bit about ORA, ORA is at the forefront of building a public health safety net for today's complex global regulatory environment. ORA professionals work in a range of program areas and locations with 227 offices and 13 laboratories throughout the United States. Six of these laboratories specialize in pharmaceutical analysis.

As the lead office for all FDA field activity, ORA serves as the eyes and ears of the

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agency through inspections of firms and establishments producing FDA-regulated products; investigations of consumer complaints, emergencies, and criminal activity; enforcement of FDA regulations; sample, collection, and analysis; and review of imported products.

ORA is committed to quality and continued improvement and maintains oversight of the industries FDA regulates, including human and animal foods and drugs; medical devices; bioresearch monitoring to support regulated products; and tobacco. ORA's efforts in these programs include collaborating with all FDA product centers and federal, state, local, tribal, territorial, and foreign regulatory public health counterparts.

We are also implementing new authorities granted by legislation and developing regulatory program standards for quality improvement, as well as establishing safety systems and coordinating emergency communications and doing risk-based monitoring of imported products. With all of these

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responsibilities, it is imperative that we work together, and our collaboration is essential to ensure that U.S. patients and the U.S. healthcare system have access to secure and consistent critical pharmaceuticals.

Within the Office of Medical Products and Tobacco Operations sits the Office of Pharmaceutical Quality Operations. In this program we have approximately 200 investigators conducting inspections as their primary function. Included in this number are the GDUFA II consumer safety officers that are funded by user fees. We have 78, and also currently we have 11 investigators that are in our foreign drug cadre.

In addition, there are other GDUFA II user-fee funded positions in ORA, including compliance officers, supervisory consumer officers, and others such as official establishment inventory coordinators. I think this allows for a total of about 40 additional user-fee funded positions.

ORA is very much involved and plays a key role in our global presence. We support training

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and staffing of the operational investigators that we have in global offices in China and India. ORA trains investigators, and these are regularly detailed to our global offices, and we assign and review inspections in the global offices.

Last fiscal year, our inspectional accomplishments included 941 domestic drug inspections and 1,045 foreign drug inspections in 59 countries. ORA has an active part in FDA's international engagements and we play a lead role in the agency's mutual reliance activities, along with the Office of Global Policy and Strategy and the Center for Drugs and Biologics and the Center for Veterinary Medicine.

As part of the mutual reliance with the EU, we are sharing inspectional findings for drug and biological inspections for products within scope, and we are in the process of assessing authorities for the oversight in veterinary medicine.

With the onset of the public health emergency resulting from pandemic travel restrictions and continued outbreak of the disease,

this has posed some difficulty in accomplishing many aspects of on-site inspectional work. As a result of these issues and the policies implemented by regulated firms restricting visitors to their facilities, we experience serious challenges in accomplishing inspectional activities.

As a result, in March, FDA announced temporary postponement of foreign and domestic routine surveillance facility inspections. From a public health perspective and as a public health agency, we are deeply committed to our responsibilities for accomplishing our mission to ensure access to safe, effective, and quality products.

We recognize this needs to be balanced with protection of our workforce, protection of the workforces of those we regulate, and also that we prevent transmission of the COVID-19 virus through limitation of unnecessary contact; for example, travel and other activities that don't promote flattening of the curve.

These postponed operations are surveillance

facility inspections that FDA traditionally conducts every few years based on risk analysis. Importantly, for-cause inspection assignments have been ongoing and have been evaluated and proceeding when deemed mission-critical, and this has been for both domestic and, where feasible and advisable, for foreign inspections as well.

Importantly, during this interim period, we've been using additional innovative ways to conduct our inspectional work that would not jeopardize public safety and are protecting both the firms and FDA staff. We are employing authorities that allow us to accomplish our work in ways that we previously have not used, such as requesting records in advance or in lieu of on-site work when travel is not permissible. This has enabled us to make risk-informed regulatory decisions and to focus and maximize the use our on-site time where necessary.

As this remains a dynamic situation, we are continuing to assess and calibrate our approach as needed, and we stand ready to resume postponed

inspections as soon as it is safe to do. In addition to the work that was not accomplished or could not be done through alternative mechanisms, we have new work that has resulted from the COVID response activity; for example, emergency youth authorizations and work supporting supply chain and access. We recognize those assignments that await resumption of travel needs strategic prioritization.

As we resume operations, we intend to apply a strategic benefit-versus-risk calculus to our inspectional work. We're using a data-driven risk assessment system that allows us to apply a strategic benefit-versus-risk framework. We are monitoring this advisory system with a goal of safely resuming on-site inspections.

In the near term, we are preannouncing our prioritized domestic surveillance inspections. We are doing this to determine the operating status of facilities and to understand the safety within those facilities, and we're using data to understand the virus' trajectory in given

localities and rules and guidelines put in place by those states and localities. I am happy to report that this week we have started some prioritized surveillance inspections.

I want to talk a little bit about how our experience through this crisis has really informed as we are moving ahead into the future. As we recognize, inspections are one among many tools that the agency uses to inform our risk-based strategy for managing quality and safety of marketed products and for overseeing the importation of FDA-regulated products.

FDA remains committed to using all of these available tools to oversee safety and quality for American patients and consumers. We will continue looking to facilitate new ways of operations to achieve efficient regulatory activities that result in the desired public health outcome.

We are committed to continued improvement and strengthen internal coordination to ensure expanded engagement with manufacturers. Considering the unprecedented workload and the

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changing priorities that have resulted from the response to COVID-19, the agency is keeping up with our user-fee commitments and our performance is commensurate with the previous year.

In addition to inspections, FDA has other tools like import alerts and heightened screening at the borders that have been utilized as part of our risk-based approach to ensuring quality and compliance. We are continuing to be committed to using these tools to oversee safety and quality of the regulated products, and we are expanding our usage of capable authority inspection reports and those inspections in third countries, looking at how we use our global partnerships and requiring other regulatory authorities.

We are looking to continue to facilitate new ways of operations to achieve efficient regulatory activities that result in the desired public health outcomes. We are committed to improvement and strengthen internal coordination; adopting regulatory efficiencies and new thinking; and looking at new tools. We look to leveraging

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technologies and having that inform our work, as well as strengthening relationships with regulatory partners to reduce redundant duplicative work and to disperse critical resources globally more effectively.

So looking at some of these tools and things that we are trying to accomplish, I think it's really helpful that we start to look at technologies and secure data platforms so that we can effectively share, access, and exchange records to inform regulatory decisions.

As I mentioned earlier, mutual reliance, we are actively evaluating inspection reports of capable authorities from their inspections in third countries, and we are participating robustly in the pharmaceutical inspection cooperation scheme, or PIC/S. The PIC/S new inspection reliance guidance has now been out since January 2019, and they're in the process of assembling metrics for the first year of implemented inspection reliance. This current COVID situation has emphasized that needed collaboration is essential.

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Furthermore, we are committed to expanding cooperation with manufacturers, working collaboratively to evaluate facility processes and look forward to discussions on ways to achieve inspectional operations in innovative and creative ways.

We look forward to engaging in dialogues and how we work best together for the best interest of American people and to benchmarking our operations against other industries and inspectorates to identify how new strategies can potentially be adopted and incorporated. And we look to have open and honest dialogue about how we function as true partners to advance medical product quality and accessibility.

Finally, as we look forward to optimizing our inspectional operations, we're going to be pushing ourselves to be forward-thinking to evaluate approaches and processes that will facilitate getting needed therapies approved and advancing access to these therapies for Americans. I think it will be important to continually closely

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engage, and I welcome the chance to have crucial conversations that we can truly get a shared understanding of where we go next.

I think these three bullets are really illustrating some areas where we could start those conversations to really understand how this pandemic has impacted and changed the generic manufacturing industry and to have conversations about how we work best together to achieve the outcomes and strengthen our partnerships so that we can truly get the best outcomes for the American people.

With that, I will turn it back to Martha. Thank you for listening.

MS. NGUYEN: Thank you, Elizabeth.

Next up, we have our final presentation before the morning break, and this will be by Ashley Boam, who is the director of the Office of Policy for Pharmaceutical Quality in OPQ.

Presentation - Ashley Boam

MS. BOAM: Hi. Thank you, Martha, and I appreciate the opportunity to be with you today.

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If we take a few moments to start and look toward the past, what we've seen a lot of is what you might refer to as a minimalist approach to quality. What that's looked like is minimal compliance with current good manufacturing practice; a reactive approach to dealing with problems that arise; fewer post-approval changes intended to improve manufacturing processes; and commonly single-entity supply chains.

What this has led to at times is outdated equipment, use of older analytical technologies, and with less robust processes, supply disruptions and, unfortunately, drug shortages.

But let's not dwell there; let's look toward the future. What we believe the future looks like is more continual improvement; a proactive approach to post-approval change management; the use of risk management plans; and a commitment to and exploring innovation.

So let me start with continual improvement. ICH Q10, entitled Pharmaceutical Quality System, actually augments the CGMP with the concept of the

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effective pharmaceutical quality system or PQS. Q10 applies to the entire life cycle of a product, so not just during development but through commercialization, and it addresses activities to manage and continually improve the PQS.

Where we see consistent implementation of the principles in Q10 is really a hallmark of what we refer to as a mature quality management system. This includes a focus on performance and continual improvement, and in particular, tracking and making changes to improve metrics that impact the patient. It also includes using data to track performance, identify opportunities for improvement, and overall to reduce quality issues that can lead to complaints, supply disruptions, shortages, and adverse events.

A little bit more about what quality management maturity looks like. Manufacturers and those who have responsibility for oversight and controls for manufacturing really take ownership for quality, and that really starts from the top with management setting the tone and investing in

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people all throughout the chain of command within the manufacturing facility.

Organizational objectives are linked to and drive quality in the organization, and the quality systems are set up to shape culture. There's a focus on innovation and continual improvement, and as I mentioned, using data to drive changes, so a performance-based quality management system with a focus on analytics and the inclusion of risk management plans and forecasting to try to minimize supply disruptions and be better prepared to ensure that reliability of supply.

Let's move to post-approval change management. Recently published is the ICH Q12 guideline, entitled Technical and Regulatory Considerations for Pharmaceutical Product Life Cycle Management, which is a mouthful. Q12 provides some important tools and enablers to help facilitate continual improvement and innovation in that proactive approach.

Those tools include established conditions, post-approval change management protocols, which

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are also known as comparability protocols in the U.S., the product lifecycle management document, and structured approaches for frequent CMC post-approval changes, which are intended to support products already on the market.

I'll spend just a moment to talk about one of the most prominent and important tools in Q12, which is referred to as established conditions. Established conditions, or ECs as we refer to them, offer applicants a real opportunity to gain clarity about their future of their application as regard to post-approval change management. It provides specificity around which elements of the control strategy must be reported when changed, but also then which elements can be managed only under the PQS without the need to report to the regulator.

It can help identify how much flexibility exists within a particular element of the control strategy and how much room there is to maneuver without needing to report a change, and then for those elements that do require changes, what's the appropriate reporting category. In general,

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established conditions offer an opportunity for additional regulatory flexibility not only in managing post-approval CMC changes within a single region, but because this is a harmonized guideline, to gain this type of flexibility in a global scenario.

Importantly, however, the ability to gain regulatory flexibility using the tools in Q12 depends on both a robust product and process understanding and that effective PQS I mentioned in terms of Q10. In particular, as you might imagine, the change management aspects of Q10 are quite important. Consistent implementation of ICH Q10 and quality management maturity provide important confidence in the firm's quality system to help support regulatory flexibility as offered by Q12.

Let me move now to innovation. You heard Dr. Kopcha talk about advanced manufacturing, and I want to emphasize that the world of advanced manufacturing gets bigger all the time. It includes, but isn't limited to, continuous manufacturing, 3D printing, innovative container

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closure systems, and more.

I'll speak just for a moment about continuous manufacturing. We've had some folks who thought that continuous manufacturing always meant end-to-end continuous processing and that's not necessarily the case. Continuous manufacturing can be applied only to the drug substance, or only to the drug product, or even simply certain unit operations within drug product manufacturing.

We acknowledge that continuous manufacturing may not be right for every product but it can certainly offer real advantages for certain products. It can minimize scale-up issues, reduce environmental impact, provide a more agile startup and changeover between products, and can provide lower costs over time. And importantly for patients, it can provide a more robust process that is less likely to experience disruption.

Now let me talk about a few opportunities for FDA and industry to continue to work together in the quality area. The first is in the area of global harmonization, which provides an important

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opportunity to help reduce regulatory burden not just for post-approval changes but also to incentivize continual improvement in innovation.

As I mentioned, ICH Q12 was finalized by ICH in November of 2019. Implementation is ongoing, and FDA expects to publish our version of this final guideline this summer. Also in development is ICH Q13 on continuous manufacturing, a revision to the existing Q2 guideline on analytical procedure validation, and a new guideline, Q14, on analytical procedure development; then ICH Q3E about extractables and leachables assessment.

There's also been an important renewed focus on quality risk management in the global harmonization space. The Pharmaceutical Inspectorate Cooperation Scheme or PIC/S, which is an international group of regulators focused on the inspection space, has recently put out a draft recommendation document on how to evaluate, if you are an inspector, or to demonstrate, if you are a manufacturing facility, the effectiveness of a PQS in relation to risk-based change management, and I

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refer you all to that very good document.

Also ICH is just beginning this fall a revision of the existing Q9 quality risk management guideline. This will also be important to supporting future continual improvement and innovation.

Now let me talk about innovation on the FDA side. When we think about how historically OPQ has assessed quality, our assessors have put together what is essentially a freestyle narrative, so lots of summarizing what an applicant has provided an application, copying and pasting data tables, and really a format that is largely unstructured text.

What this makes challenging then is knowledge management, managing consistency and quality across the life cycle, and in general, it hampers our overall modernization of our assessment process. What you heard from Dr. Kopcha is our ongoing efforts and development of the KASA system, which is intended to address this.

The KASA system is being designed to capture and manage knowledge during the life cycle of a

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drug product and it includes rules and algorithms that help identify risks to capture risk mitigations and to facilitate consistent communication to applicants regarding issues related to the drug product, the manufacturing process, and the facilities.

The KASA system provides a computer-aided analysis of applications to help compare the information provided against existing regulatory standards and our understanding of quality risk across our collection of approved drug products and facility information. Then it provides a structured assessment that cuts way down on the text-based narratives and the summarizing of information from applications that makes for a more efficient process for our assessors.

Where we are currently is that we've really done a lot to be building the house, the knowledge-aided assessment piece. This piece, as you heard from Dr. Kopcha, is current state, and we are putting this in place for more and more dosage forms and more and more of the subdisciplines of

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quality. But as you see here on the left hand of the slide, we're still relying on manual entry of unstructured data extracted for our submissions. The exciting piece is the future, which is where we'd have structured information submitted by an applicant through our gateway that would automatically filter into the KASA system and facilitate the analytics and the algorithms that we have in place.

In conclusion, as you've heard from other speakers, our success really depends on FDA and industry working together, as well as with our global regulatory partners to achieve the future of pharmaceutical quality, which we believe includes more robust manufacturing processes, a culture of continual improvement and innovation, fewer supply disruptions and drug shortages, which then lead to more consistent access to important medicines for patients.

Thank you very much for your attention today.

MS. NGUYEN: Thank you, Ashley.

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We will now take a break until 11 a.m. when we will resume with additional presentations as part of this public meeting. I have two quick reminders. One is if you joined this meeting by phone, please mute your phone. Second, if you would like to speak during the open public comment period, please send a request to either Dat Doan or indicate your request in the technical support chatbox before the lunch break. With that, we will take a break until 11 a.m.

(Whereupon, at 10:28 a.m., a recess was taken.)

MS. NGUYEN: Good morning, everyone, and welcome back to FDA's virtual public meeting on the Reauthorization of the Generic Drug User Fee Amendments of 2017 or GDUFA. My name is Martha Nguyen, and I will be moderating this meeting. I want to thank all of the FDA presenters this morning, and thank you to all of you for participating in this meeting virtually.

We have one more FDA presenter this morning, and then the rest of the morning will be dedicated

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to presentations by other federal agencies and trade associations. As a reminder, we will have an open public comment period this afternoon. If you would like to speak during that open public comment period, please send a message to Dat Doan or in the technical support chatbox before the lunch break so that we can arrange for your participation in that way.

Next up, I would like to invite Rob Lionberger to speak. He is the director of the Office of Research and Standards in OGD.

Presentation - Robert Lionberger

DR. LIONBERGER: Thank you, Martha.

It's my pleasure to talk to you this morning about the pre-ANDA program and the activities related to complex generics. Hopefully, as many of you who are experienced with the GDUFA II program knowthere are multiple elements of our pre-ANDA system.

There is our science and research activity, which provides the foundation. There are product-specific guidances, which provide clear

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advice for potential applicants. There's a significant controlled correspondence program that provides quick answers to specific single questions, and then new in GDUFA II, we have a pre-ANDA meeting program for discussion of more complex issues related to complex products.

As part of GDUFA II, GDUFA II defines the class of complex products specifically to focus the pre-ANDA meeting activity around those complex products. So I'm not going to go through in detail exactly what's a complex product. It's a little bit simpler to talk about the things that aren't complex products.

The simpler products, the non-complex products, essentially are tablets, capsules, suspensions for oral administration that acts systemically, as well as almost all of the solutions for various routes of administration, including oral and parenteral solution.

If you take those very standard, simple dosage forms, that's essentially this class. Almost everything else is a complex product.

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That's probably the simplest way to think about the division. Although complex products are very important, as I'll show in this talk, most of the work that FDA is still doing is on the non-complex products. They still make the vast majority of the generic products that are being submitted and supplied, so it's important to keep that in mind as we go through these activities, that there's a valuable part of maintaining appropriate advice on the non-complex product as well.

I want to talk a little bit about how the overall system works together. You've heard a little bit about this from Sally and Mike, about the importance of the research activity and how it feeds into the different activities, so I want to emphasize that a little bit by walking people through how the pre-ANDA system works from FDA's perspective, beginning with research and moving toward application evaluation.

Again, research planning, we have to decide what research to do. One important part of GDUFA is that there's been, since GDUFA I, a public

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research, public workshop, and a public process by which we seek stakeholder input on which research activity will be important both to our industry stakeholders and to our patient stakeholders through public health advocates. We have a long-standing process for public input into the research planning. We also have ways in GDUFA II where we meet regularly with the industry stakeholders to discuss and align a research plan for those activities.

We also look at the inventory specifically of complex products to say what products are complex and which ones will require some research activity before we can provide clear scientific advice on how to develop generic versions of those products.

Once the plan is complete, there's a lot of work that goes on in executing the research. Research at FDA is done either internally, so the FDA labs in the Office of Pharmaceutical Quality and also in the Office of Translational Science; work on that. We also internally do a lot of data

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analysis and model building, but there are certainly some things where we don't have either the capability or capacity to do internally, so we collaborate with academic experts.

We bring in leading pharmaceutical scientists across the world and engage them with the generic drug program. This builds a reservoir of expertise of people who because of their participation through this collaboration have much more understanding and expertise of issues related to generic drug development, and students who work for these collaborators are part of the pharmaceutical sciences workforce who have experience in things related to potential generic drug development so this isreally expanding.

Also in addition to accomplishing the research goals, it also expands the scientific pool of experts who are available to the community as you're developing the product. That's had a significant impact on raising the visibility of the scientific issues related to generic drug development when the leading pharmaceutical

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scientists are collaborating with FDA and addressing them. That's maybe under-recognized but an important part of our program.

As well, some of the activities that we do externally, FDA does not have the capability internally to do human subject research, so some of our grants and contracts go for human subject research to obtain new in vivo data that helps the research program, and we have activities related to oversight and monitoring and protecting the human subjects engaged in those research activities.

Once the research is complete, then the staff within FDA, basically what we do is digest the results of those research activities and use them essentially to create research and standards. The office that I lead is the Office of Research and Standards. We do the research, but our goal also is to translate that into advice for the development of generic products. Certainly, they're not standards in the formal sense, but they form the scientific advice.

You see many of that in our product-specific

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guidance on complex products. We also say how do we take this research and put it into a form that can be useful for pharmaceutical development and evaluation, so that's the new tools and bioequivalence approaches.

There are additional ways that applicants can engage with us on these activities, primarily on complex products through the pre-ANDA meetings. So all of the knowledge that's been developed through the research program thinking about product-specific guidances also feeds into the pre-ANDA meeting response, so it's built on that foundation.

The pre-ANDA meetings are very company and product specific, but we also try to do general communications through industry workshops such as our SBIA workshop on complex generics that we hold every September with about 3,000 people attending that each year, as well as training internally for FDA staff so that the knowledge that we generate through this research activity flows into our review process.

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The final step -- and this is one where I think that there are opportunities for improvements in the future -- is really how we assess the applications once they come in. Certainly within our internal processes, the experts who have been thinking about these products get consulted and bring that knowledge into the ANDA review assessment.

For example, the OPQ laboratory scientists who've done incredible work on the abuse-deterrent formulations, they're involved in the assessment of the in vitro data for the abuse-deterrent properties. As well, when we develop new modeling simulation approaches to BE studies, those people are consulted through the ANDA bioequivalence review process. So the experts are brought in as needed, and then this again leaves to application decision.

The important thing is that there's a pipeline of activities wherein GDUFA I really establishes that you have a research program. GDUFA II adds on goals around product-specific

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guidances and the pre-ANDA meeting process as we look forward and say how do we continue this activity flowing through into application decision processes.

I just want to talk a little bit about the different aspects of the program briefly to give an idea of scale and impact of the program. For research activities, with the stable investment from GDUFA II, we're able to have a very active research program. There's probably about a hundred active projects both internal and external at any time.

We publish each year a list of the new grants or contracts where we go outside, so we're completely transparent about the contracts and grants that are awarded each year, and we have a website where we list all the publications and presentations that come out of this process. We have approximately -- although I think it's been left off of the PDF slide here -- each year 50 peer-reviewed publications, around 100 presentations at different scientific meetings.

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You can go to our website to the provided links to where those are, as well as we develop our own focus workshops either run by FDA or are collaborators within CDER to the SBIA group, or with external scientific organizations, depending on the topic and the focus, to provide detailed insight into some of the specific areas. So we look for the appropriate audience for each group.

Again, the key scales, the research activity, probably the first place from a regulatory point of view, you'll see the research impacted through the product-specific guidances for the complex products; and this again, here's the publication and the magnitude that you can see for these activities.

Just to give some examples of the kind of things that are covered by the research example, we've divided the research approaches into three broad categories. One is about generic access and all product categories. This is probably the largest chunk of our research program. It's focused on what's the best way to demonstrate

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bioequivalence for complex and locally-acting products.

This includes a lot of the in vitro BE methods, so there's a lot of interface between the product quality evaluation, the bioequivalence evaluation, and these areas for the new approaches to topical semi-solids; nasal suspensions; ophthalmic suspensions and emulsions; and inhalation products. These are things we talk about at our public workshops each year.

Another category of research helps build the confidence in generic substitution. These have been things that primarily during GDUFA I we began many of these because there was a lot of questions at that time about brand to generic switching and is it effective.

So we really did some focus studies in patient populations that looked at brand to generic switching and patients switching back and forth, really showing that, as we expect, based on our approvals, that the generic products are substitutable in the patient population.

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This can be important. Some of these very significant ones on antiepileptic drugs helped change the perspective of some of the professional societies that had perhaps sometimes a negative view of generic substitution. So there's work like this that help build the confidence broadly in the generic drug substitution.

We've also been involved in adapting surveillance tools for generics. The post-approval questions about generics are very different than those for new drugs. At FDA, our Office of Surveillance and Epidemiology is looking at unexpected adverse events for new drug products that raise safety issues that weren't discovered in the NDA approval process.

For generics, we're really looking at questions about substitution and are products being successfully substituted, and sometimes that's a more subtle question, less than a large effect than a new unexpected adverse event. So there are different types of tools and methods that might be used in that as the generic industry thinks about

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how its pharmacovigilance program should look in the future. There are new approaches. There are lots more data available and different suppliers of that type of data. FDA has a Sentinel program and there's interest in real-world evidence.

So a lot of things like that feed into this approach to say what should you do to ensure that generic drugs are being successfully substituted the way we expect.

The final category is focused less on the product categories but on the tools for development and review. There are two big categories that we focus on here. One is modeling, simulation, and data science. These are PBPK models, absorption models, and clinical trial simulation models, as well as the new frontiers in data analysis, machine learning, and artificial intelligence models and applying them to problems relevant to generic drug development. We have one paper that talks about how you use machine learning models to predict ANDA submission probabilities that we'll see an NCE [indiscernible] application come in.

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Finally there's characterization, advanced analytical characterization. A lot of this is done with FDA lab. One specific example is looking at long-acting injectables, a product category that has a very small number of generics and a lot of complicated polymer characterization issues related there that come out of our research programs. These are the scope and type of things that are involved in the research activities, and they feed the development of products through the guidances and our discussions at pre-ANDA meetings.

Talking about our product-specific guidances, this is a long-standing program that predates GDUFA II. Currently, there are about 1800 product-specific guidances available. We now, with the GDUFA support for this program, are really able to deliver on consistent quarterly postings of new guidances -- this is really I think important -- to the generic industry as a whole.

These guidances are incredibly useful to having an efficient review process, especially for the more straightforward process. Within the

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Office of Generic Drugs, our Office of Bioequivalence generally has a very high first-cycle acceptability rate for the bioequivalence review primarily because most of the applicants look at the guidances and follow them. They're very clear about what the expectations are for the bioequivalence studies. We try, as much as possible, to reduce ambiguity through the PSG process, so I think this is a very successful program overall.

What's new through the GDUFA support for research is the extent of the guidances that cover the complex product. You can see that in FY 2019, there are 24 new guidances for complex products and some significant updates for some of the transdermal systems, and a large amount of updates with keeping the complex product guidances up to date in that area.

Some of the trends in the product-specific guidances that we see, again, there's a continual flow of guidances for the complex product. The program began in 2007, really filling out the solid

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oral products and the straightforward BE guidances and very effective and useful for our review efficiency there, but the movement in the future is toward the product-specific guidances.

For example, in FY 2019, if you look at our complex product guidances, 30 of the new or revised guidances provided an alternative bioequivalence approach that was much more efficient than the one before, so generally providing an alternative to a clinical endpoint bioequivalence study. So these come both sometimes in new guidances, where the first appearance has an alternative, but also some of these are revisions where when we revise the guidance, we're able to provide these new opportunities.

As we look at this and reflect on this, as the large number of products and the guidances are available, some of which date back to even before the first postings in 2007, there are maintenance costs to keep all these guidances up to date. Applicants need to have confidence that these guidances reflect our current thinking, so there's

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continual work that we do. That's why every quarter you see revisions to this as well.

As part of the goals system, the GDUFA goals for the PSG program talk about goals for the non-complex NMEs and having them available two years before the first legal submission date, but there's no specific goals related to complex products, although there's a significant amount of activity related to that. But there's no certainty on when the complex guidances will appear in the current system.

The other aspect of our pre-ANDA program is our controlled correspondence process. This is a long-standing process. It dates back to almost the beginning of the generic drug program in the 1990s, that often Generic Drugs has been answering written questions from applicants about controlled correspondence.

What we've seen through the GDUFA I and II years is this program continues to increase. Between 2015 and 2019, the number of controlled correspondences has doubled, so there's a lot of

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interest in applicants getting answers to these questions. There's a broader group of companies that are asking these questions. This is an important part, and this is probably the most efficient way that a company is going to get an answer. There's a 60-day goal for most of these, so it's the fastest way to get information about generic drug development. But there are costs associated with this, and it's something that seems to be continuing to increase in the workplace.

Just a few analysis assessments; about 40 percent of these controlled correspondence questions are about things that fall into the complex product category, so that's part of the reason for the growing aspect of that.

In GDUFA II, we have something called a complex control, which is not, unfortunately, about a complex product but it's about a complicated issue, so there's a nomenclature issue there that maybe we can resolve for clarity. But about 7 percent of the controls fall in that category with a 120-day goal date. The other 93 percent get

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answers within 60 days.

This is a significant part of the pre-ANDA program. Still the majority is related to the non-complex product, and generally many of those are Q1-Q2 questions, which even though they're about simple products, sometimes can raise different scientific and regulatory challenges as well.

To move on to the pre-ANDA meetings, which were introduced formally in GDUFA II with goals and commitments, what we've seen is prior to the goals and commitments, we received about 30 requests each month, and that's the first year of GDUFA II. It almost tripled a little bit more the next year, so a great uptake of the program.

Use continues to grow, but we've been prepared for this. We expected this. We were able to meet all of our meeting goals related to the pre-ANDA meetings. I think this is an important effort that the program has made. If you look at other user-fee programs, sometimes the meeting goals have provided challenges in those programs,

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but for GDUFA, we've been very successful in that way, and that's in part due to how we've negotiated and built up the program slowly, but we're mindful as meetings grow that there are going to be challenges to make sure that we continue to maintain appropriate performance.

Again, the pre-ANDA meetings, these are really a place for innovation in bioequivalence approaches. One of, I think, the great things about the GDUFA II commitment letter is that it's really said explicitly that if there's a product-specific guidance and you want to do something different than a guidance, you can come in and discuss that through the pre-ANDA meeting process.

I think one of the challenges in generic drug development is oftentimes industry will say FDA guidances, they're the law, they're the rules. Really, our guidances are scientific advice. Every guidance we write says that alternative approaches that meet our statutory and regulatory requirements are acceptable, but oftentimes the perception of

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FDA is, no, that's not the -- people in the industry think of guidances differently than that.

Pre-ANDA meetings, by explicitly saying you can come in and talk to us about an alternative approach I think really implements that principle that alternative approaches are viable and accessible. I think that's an important aspect of industry and innovation to provide a place to get scientific feedback and alignment on new approaches.

Just thinking about the return on the investments in the pre-ANDA program, by far the vast majority of the GDUFA user fees really go to support our ANDA review process. There are thousands of applications a year. That's a huge program. There are thousands of people working on that.

There's a relatively small group of people doing research on the pre-ANDA programs, running pre-ANDA meetings, and engaging that, but that really has an outside impact because what that small set of activity is targeting is really a very

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large potential market opportunity for the generic industry of complex products that currently don't have generic competition. So these are also, I think, areas where our patient and stakeholders would be very interested in having generic competition for that.

So there's a huge area where this investment is focused on, an opportunity for significant leverage and future opportunities there as we look at the scope and scale of that that remains.

Even with all of the successes of the generic program, there are still products without generic competition. The brand industry -- good for them -- are not standing still. They continue to develop new products, whether improvements or competitors to existing products that now are subject to competition. So this area doesn't keep shrinking. It at least stays maintained and in place. So there's a constant focus on what's the future competition going to be like.

When we look across the different areas where we see this, all of the top 10 areas where

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we're looking at research activity, each one of those is from some significant subset of that area: the complex active ingredients; looking at immunogenicity for small peptides where there's no generic competitors; topical dermatological products; inhalation; ophthalmic; nasal; complex injectables; long-acting implants; and more complex drug-device combination products.

Again, each of these areas is a sizable chunk of those potential markets. We try to focus our activities on things which will enable competition and be active in the future. This is where we get valuable feedback through the GDUFA I public meeting process and the GDUFA II yearly meetings with industry working groups on regulatory science, and it helps keep us focus on the complex product categories where potentially there will be future generic competition.

As we think about it from the public perspective, the return on research investment to our public stakeholders also depends on successful ANDAs, so moving things fully through the pipeline,

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the science and research, the guidances, having meetings on development, and getting generic companies in development. But our patient stakeholders, what really drives their return on investment is the successful ANDAs.

As you look at this chart here, as the number of generic products increases, the savings to consumers increase. If you have a very small number of competitors, there are limited savings. As competition increases, the savings increase greatly in these areas.

For example, in areas where the scientific advances are able to really change the paradigm for bioequivalence -- we have an example -- one of the first topical products where we provided an in vitro alternative to a clinical endpoint study was acyclovir ointment. This was really the very first thing that we were able to move forward there.

Through GDUFA II, we've moved this through a broad category of the topical products, but with the longest one, you can really see that since

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2012, 27 ANDA submissions and 13 approved ANDAs really pushed the curve for that product very far down and really changed the dynamics of competition in that environment with these novel approaches to complex products.

That's one specific example, but I think we'll be seeing in the future that as these in vitro BE approaches propagate through guidances -- 30 new in vitro approaches were added to product-specific guidances last year, so that's 30 cases that could end up changing market dynamics like this.

If you think about what the future environment will look like, there's still a gap. If we look at our complex product definition, about 30 percent of the potential reference-listed drugs are for complex products. Most recently about 12 percent of our approved ANDAs are for complex products. So again, as things pull through the pipeline, there are opportunities for -- if the number of ANDAs just balances the number of reference products in this particular category,

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there's still a lot of growth for the complex product.
What you see from this is that probably in the future, the fraction of the ANDA review work focused on complex products will likely increase. This is an important thing to keep in mind as we develop what the systems look like in the future. The key is to keep complex products moving through the system, identify places where they need additional activities, and also to think about the resources that will be needed for the ANDA review program in the future.
Other aspects of the future environment, brand companies aren't standing still. They're developing new types of products. I've put two visually interesting products, and one is a nasal implant product. I put the picture there to look like a space alien landing, but there are novel things that are happening.
There's also a Soft Mist inhaler. Twenty years ago, there were dry-powder inhalers and the aerosol metered-dose inhalers. There's now a third

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category of inhalers, the Soft Mist inhalers that have different categories and performance tests. We have extremely active research programs and pre-ANDA meetings on this new class of inhalation products, so our research and our guidance developments need to continually keep pace with the new products that are being added into the pipeline.
Finally to conclude, the pre-ANDA system provides clarity and can improve development efficiency. It's still new, just three years of experience with GDUFA III. Certainly, the industry has to adapt their product development systems to use this program most efficiently. So there are lots of ways that we can, I think, work together to identify ways to make this system work even better.
The research is really important to keep the pre-ANDA system working. When you have a pre-ANDA meeting, because we've been engaged in the research activities before the products come in, we have expertise, and there's expertise also available in the community focused around this.

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So there's an essential part of the research activities in making this work well and treating the guidances. And again, the meetings really support innovative approaches that can accelerate access to complex generic companies that want to be first. You can use the meeting process to even get ahead of our product-specific guidances. You don't have to wait for a guidance to do something innovative. I think that's a great feature of the program that can drive new approaches to bioequivalence.
So with that, we'll continue with our meeting, and hopefully this has given you an overview of some of the key aspects of our complex generics and pre-ANDA program.
MS. NGUYEN: Thank you, Rob.
Rob's presentation concludes our planned remarks by FDA officials. The remainder of this public meeting is dedicated to receiving feedback from stakeholders on the reauthorization of GDUFA. After each presentation or group of presentations, I'll give the FDA panel of experts and opportunity

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to ask any clarifying questions of the presenters.
Finally, before I announce the first of the speakers from the other government agencies, I wanted to put in one last call for public comments. If you would like to provide public comment this afternoon, please send a message before the lunch break to Dat Doan or put a message in the technical support chatbox so we can make arrangements for you to speak. When we break for lunch, registration for open public comments will close.
Next, I'd like to invite Dr. Jeff Kelman, the chief medical officer at the Centers for Medicare and Medicaid Services, to speak. Jeff does not have slides, so participants should see a single slide that will not advance during his remarks.
Presentation - Jeffrey Kelman
DR. KELMAN: Thank you, and thank you all. I'd first like to thank the FDA for inviting me to participate in this panel. As we in CMS are likely the largest single payer for drugs in the country, we take the GDUFA process very close to our hearts.

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I'm going to discuss briefly the role of generic drugs in the Part D Medicare program. To cut to the quick, all our enrollees in the Medicare program benefit from FDA's continued efforts and efficiency in bringing generic products to market. The benefits, the Part D benefit, has been in existence since 2006. Before then, Medicare covered some Part B drugs, so-called, which are doctor administered, hospital administered, and some nebulizer administered, and essentially no retail drugs at all except transplant drugs.

Currently, we cover approximately 1.5 billion prescriptions per year -- that's billion, not million -- and in terms of data collection, we see over 35 billion data elements in Part D annually. The gross drug cost in Medicare Part D grows more than 165 billion per year in Medicare retail and specialty pharmacy, self-administered drugs.

Of those prescriptions, generic drugs, as defined by approval under an ANDA, account for 80 percent of all prescribing events while also

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accounting for less than 20 percent of GDC, gross drug cost. Of note by the way, the Part B drugs account for 35 billion in 2018.

Part D formularies are in general 4 or 5 tier, depending on whether there are 1 or 2 generic tiers. The most common design is preferred generic/non-preferred generic, preferred brand/ non-preferred brand, and specialty tier. Co-pays and cost sharing are dependent on tier placements.

In general, the specialty-tier drugs costs are commonly a percentage of co-pay, between 25 and 31 percent maximum, depending on the extent of the deductible. Non-preferred brands are mixed between a cost sharing and fixed co-pay, but preferred brand and generics are generally a fixed co-pay.

There's the added protection, by the way, for low-income subsidy patients, which is about 20 percent of total enrollees, so minimal co-pays between $4 and $10 per prescription filled. There's also a catastrophic safeguard for everybody that reduces the co-pays to 5 percent or less after the catastrophic threshold is reached.

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From the start of the program, generic drugs have been a central feature of the benefit design. The generic dispensing rate, GDR, as defined as percentage of total prescribing events filled by drugs approved in an ANDA, has been climbing slowly since the beginning of Part D and now exceeds 80 percent. This rate is obviously highly dependent on the FDA approval of generic products, which is why we take the GDUFA process so seriously.

The generic substitution rate, which is a measure of use of all generics, or use of generics I should say for those drugs that had a licensed generic available, is now greater than 90 percent. Interestingly, the factors that determine the generic substitution rate are not completely clear, as the substitution rates have been slightly higher in the low-income subsidy population than in the non-low-income subsidy population, which in theory are exposed to much higher differential drug costs by not using generic equivalents. This has been true regularly for the last seven years.

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In practice, the goal of identifying savings in drug expenditures by increasing GDR and GSR needs to be examined carefully. I'm always told that we should really encourage more generic dispensing as it would solve the drug cost problem. In reality, with significant generic penetration of a market, the brand drugs that remain are often priced at a generic level.

The functional generic, GDR, by the way, in that case that would generically price ANDA-approved drugs counting as generics may be significantly higher than reported. Similarly, increasing the GSR may have a limited cost impact if it's the therapeutic equivalent of ANDA drugs already deeply discounted.

Savings are clearly found in new generics, especially for higher cost non-biological specialty drugs. Note that this is a discussion of savings and potential savings from biosimilar drugs -- from non-biosimilar drugs. The biosimilar subject is beyond the scope of this presentation, but actually are very interesting.

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Following the FDA standards for formulary purposes, we count generic products as absolutely therapeutically equivalent to the originators. The addition of a generic to a formulary is considered a maintenance event. It is not changing the basic structure or value of the formulary and only having a potential positive effect on beneficiary cost sharing because of the addition of a drug to a generic cost here in exchange or in addition to the brand drug tier that was being paid.

Therefore, new generics can be added mid-year with the optional removal of the brand drug. We don't allow this for non-generics. We have found this to be very important for early market penetration, especially during a time of limited exclusivity period.

While the use of generic drugs only impact one segment of Medicare drug costs, I always like to point out that the basic premiums of Part D have actually fallen over the past five years. It was $32 per month in 2016, down to $27 per month in 2020, while the overall drug portfolio has clearly

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expanded. At CMS, we consider the FDA generic drug approval process as the key element in Part D success. Thank you.

MS. NGUYEN: Thank you very much, Jeff, for your remarks at our public meeting.

Next, I would like to invite Peter Glassman from the Department of Veterans Affairs to present.

DR. GLASSMAN: Hi. This is Pete Glassman. Can you hear me?

MS. NGUYEN: Yes, I can.

DR. GLASSMAN: Wonderful. I don't see my slides up just yet. There we go.

MS. NGUYEN: Sorry to interrupt you. You should be able to advance your own slides by pressing on the right arrow on the bottom left of your slide deck. Do you see that?

DR. GLASSMAN: I do. Thank you.

Presentation - Peter Glassman

DR. GLASSMAN: I am Peter Glassman. I'm the chair of the Medical Advisory Panel for Pharmacy Benefits Management Services for the VA. For some quick disclosures, part of the angle of which I

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come from as the chair, I'm the co-director of the VA Center for Medication Safety. Just to point out, the center works with the FDA on various medication safety issues. I'm a physician and I work in Los Angeles. I do primary care and palliative care. I'm also an academic, and I'm a VA representative on the Drug Safety Board for the FDA.

From our perspective, when we create our formulary, which is somewhat different than the structure in the private sector, our formulary goals are very similar to others, which is an evidence-based formulary.

We want to promote appropriate drug therapy; we want to reduce geographic variability across our system; and we want to provide an affordable and uniform drug benefit, especially because we exist across the country in VAs. There are obviously other reasons we have a national formulary or other activities we do for the national formulary, which are listed on the right.

The VA is a large healthcare system in

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fiscal 2019, and we'll go into this a little bit more during my brief presentation. We provide a great deal of 30-day equivalent prescriptions, almost 300 million. Most of that is through mail order with a small amount locally distributed. You can see our drug budget, and not surprisingly, the VA takes care of a mostly older male population with multiple comorbidities, which most of you know.

Over a period of time -- this is roughly 20 years, a little less than 20 year, about 18 -- you can see that the number of pharmacy uniques, which is the number of patients who use our pharmacies, has gone up from a little under 3.5 million to little over 5 million.

When we look at value, it's really the intended outcomes more so than benefit over cost. As that net benefit or intended outcomes improve relative to the cost, you get better value. As intended outcomes or net benefit remain stable or improve with lower costs, you indeed get better value.

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Generics, provided they're safe and effective, which is really what we're talking about today, provide similar outcomes to the originator products at a lower cost and they provide better value. As a general rule, as you've heard, the value tends to increase as generic competition increases and pushes prices downward.

I just wanted to show you a little bit more on those prescription trends. You can see over a period of time, roughly speaking, about 20 years, the 30-day equivalents are in the upper bar and the total prescriptions on the lower. Clearly, it has gone up substantially over the period of about 20 years, the last 20 years.

At the same time -- not surprisingly, given that there are new drugs being developed and new drugs being used -- the costs have gone up substantially over that roughly same period. As you can see, they are around 5.5. You can see the lines diverge a bit because of the hepatitis C drugs that were being used during this period to a large extent. The lower line would be the drugs

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without the hepatitis C, I believe.

Yet, at the same time, we've had a relatively -- I won't say flat but a relatively flat 30-day equivalent prescription drug cost. You can see the rise, again, over that period of 20 years has gone to where it is now but really kept under reasonable control of costs over that time period.

This slide really is to highlight the fact -- and we'll get into this a little bit more in a few slides -- that the VA really is a generic-oriented pharmacy benefit. You can see in this particular study done by Walid Gellad in 2013 or published in 2013. You'll see the VA, compared to its Medicare cohort comparators, uses a great deal more of generics or less brand, and this is diabetic care.

Just to highlight, generics provide VA savings, allowing funds to be used elsewhere in two general components. One is obviously after a brand goes to generic, after the exclusivity period. Also, whenever possible and when it's available,

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contracts are established for sole generic products. That generally reduces costs further through competition, competitive bidding, and helps provide uniformity across VA, which is really important in general but also particularly for certain drugs such as an anticoagulant such as warfarin.

I just wanted to highlight the patient perspectives. We do have a tiered co-payment system and prefer generics that are less expensive than other non-preferred or brand name drugs typically, and there's just a little bit more information about that.

To really look at this a little bit more closely -- and keep in mind this data may not be exactly to the database limitations and separating out some of the generics and brand products -- you can see that a large proportion of the drugs that we use in VA are obviously generic, and there's a small proportion of brand and over-the-counter drugs. On the next slide, though, you can see where that flips. Again, keep in mind the database

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limitation, but you can see where it flips in terms of the cost.

I think we have to keep in mind -- and this has been mentioned earlier as I recall -- there are other considerations that may affect the generic market; quality issues, for example, on precursor chemicals or the active molecule. We've seen price gouging in the past, especially when there's a lack of competition, and there are shortages from various causes.

The VA has other special considerations that it has to keep in mind when it brings in generics, which is these must be Trade Agreements Act compliant unless a waiver is granted. In order to be added to a VA contract, GNP status, based on FDA inspection, needs to be confirmed.

I just wanted to point out that part of the ability to control costs and provide quality care is dependent on our access to safe and effective generics. These generics in turn provide excellent value to the VA, to VA PBM, to our patients, and to the U.S. taxpayers, allowing access to numerous

pharmaceuticals at a reasonable cost.
Thank you, and thanks to the FDA for allowing me to speak today, and thank you to my VA PBM colleagues who helped me with information and slides. Thanks so much.
MS. NGUYEN: Thank you, Pete.
The final of the presentations by federal agencies will be given by Chris Lamer from Indian Health Services, after which I'll give the FDA panel an opportunity to ask questions of all three presenters.
(No response.)
MS. NGUYEN: Chris, have you joined us?
DR. LAMER: Oops. I'm sorry. I'm talking away here, and my mute must have clicked off and back on again. Let me run back over this again.
Presentation - Christopher Lamer
DR. LAMER: I'm Chris Lamer, and I'm with the Indian Health Service. We are an agency under the Department of Health and Human Services, and we're made up of federal direct service programs, tribally-operated health services, and urban Indian

Health Services. The mission of the Indian Health Service is to raise the physical, mental, social, and spiritual health of American Indians and Alaska Natives to the highest level.
We provide healthcare services to over 2.5 million people from 573 federally recognized tribes across 37 states. All of the references I have here are a bit older. Chronic diseases are prevalent and contribute to the leading causes of American Indian and Alaska Native deaths. In fiscal year 2018, there were nearly 13 million outpatient visits, many of which involved prescribing chronic medications, most of which are generic.
There are many benefits in the use of generic medications within our agency. The increased flexibility to select a medication from a variety of manufacturers provides our programs with the opportunity to select those that are priced lower. It also allows us to continue therapy during a manufacturer's recall when other options are available.

Lowered costs from competition is one of the greatest benefits to us because the lower costs enable our programs to increase access to pharmacological therapies for American Indian and Alaska Native people. And finally, the knowledge that the manufacturing distribution of generic medications is overseen by the FDA helps to assure safe and efficacious therapies.
My last slide brings up some areas where we would like to see some improvement, but we appreciate knowing generic medications are safe and free of contamination and that there are often multiple manufacturers that can provide these products.
The widespread recalls such as those seen with ranitidine and metformin ER have significantly impacted our healthcare programs and patients. This has resulted in an increased workload, changes in medication treatments for our patients, and sometimes confusion or concern among patients.
Finally, we recognize that biosimilars are not the same as generic medications. Their status

as something new brings uncertainty and confusion to our prescribers. We'd like to see increased awareness of biosimilar products as well and how the FDA assures their safety and efficacy in the hopes that biosimilars, like generic medications, can help increase the access of these treatments for our patients.
With that, thank you very much for the opportunity to provide some feedback, and I hope you all have a wonderful day.
Clarifying Questions from the Panel
MS. NGUYEN: Thank you, Chris, for your time and for your presentation, and thanks to Jeff, Pete, and Chris for all of their feedback.
At this point, I'd like to pause to give the FDA panel an opportunity to ask questions. I will moderate this by inviting individuals to voice their questions. I would ask each person to give their full name so that the presenter knows who is asking the question. I think the first question will come from Maryll.
MS. TOUFANIAN: Good morning. This is

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Maryll Toufanian, director of the Office of Generic Drug Policy. Thank you to all three of our federal partners. I feel like I want to add you to the circles of activity that I described earlier today. I have a question for each in turn; and, Chris, your last point triggered this for me.

In addition to our activities in approving generic products, are there steps FDA can take to help facilitate your individual entity's administration of your programs? Specifically, are there any steps related to transparency, or regular activity, or enforcement activity; anything that we can do to support you?

DR. LAMER: This is Chris Lamer, and I thank you for the opportunity to comment on this. As a member of the Drug Safety Board, I do appreciate the open awareness and communication of things that are taking place within FDA related to medication safety and continued participation in that program would be very helpful.

As far as transparency, I think the FDA has been very transparent and open, both to federal

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partners and the public, about the happenings taking place. I can't think of anything off the top of my head that I would make as a recommendation.

DR. KELMAN: Hi. This is Jeff Kelman. I agree. The FDA has been highly transparent and very active in promotion of generic drugs and approval of generic drugs. If anything more can be done, I would prefer it in the region of beneficiary education because we still get resistance from beneficiaries, not to mention physicians, who don't feel or don't trust generic drugs, and that's a costly mistrust for us. Thanks.

DR. GLASSMAN: I echo both those comments. I don't have anything particular to add, but I think those are really on point. Thanks.

MS. NGUYEN: Thank you

MS. TOUFANIAN: Thank you.

MS. NGUYEN: Next, we have a question from Jacqueline Corrigan-Curay.

DR. CORRIGAN-CURAY: Hi. This is Jacqueline

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Corrigan-Curay, Office of Medical Policy, and I think this somewhat follows on some of the answers in the questions that Maryll had just expressed. Certainly providers are often independent thinkers, and it's not price that they think about first.

What has been successful in leading -- obviously, many of your providers are willing to prescribe generic drugs and realize the value. So what are the messages and things that FDA can do or has done, as well as our industry partners, to continue to give providers that confidence to prescribe generic drugs when they are available for their patients?

DR. LAMER: This is Chris, and I think that within the Indian Health Service, the FDA and other programs have done a great job at promoting generic medications. For us, we focus on generic names, generic products, and those are our primary medications when available.

Sometimes there is confusion among patients, especially with advertising, where there are brand names and generics, and they don't feel that

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they're getting what they are expecting to get. But other than that, as far as generics go, we have I think a very good foundation and comfort level.

The biosimilars, again as I mentioned on my last slide, are an area of opportunity to promote increased trust in these products. Many people do not seem to understand the differences between a biosimilar and a biological, and the similarities as far as efficacy and safety are pretty much the same. So I think an increased message on that aspect would be helpful.

DR. KELMAN: This is Jeff. From our point of view, academic detailing of generics with the FDA standing in the place of the academic world would be helpful, and particularly detailing down to the beneficiary level.

The question of biosimilars is really a whole another panel because we find that physicians don't treat them as interchangeable, and they're not interchangeable. But they don't treat them as a therapeutically equivalent module, and that I think is going to take specific detailing by the

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FDA down to the provider level.
DR. GLASSMAN: This is Pete Glassman. Again, I would echo the comments beforehand. I would also add that as people have gotten comfortable with, and certainly were comfortable with, generics in the VA, because we're a generic-based system and we use generic names similar to the IHS -- as people have become comfortable with generics, it's become less of an issue. But I think the real key would be, at a transition point, when a drug is moving from brand to generic, that I think is the time to really highlight the similarities between a generic product versus the prior innovator brand.
I think it's similar for biosimilars. I think it will be kind of the same case scenario for biosimilars. I think a lot of people are confused perhaps with what a biosimilar is, and I think that highlighting, as these biosimilars are coming out, what they are and how they work would be really advantageous to the public, as well as to providers, as to that transition period, and to

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educate during that time. Thanks.
MS. NGUYEN: Next we have a question from Ted Sherwood.
MR. SHERWOOD: Thank you. Are there other areas for us to consider as we enter another round of GDUFA negotiations?
DR. GLASSMAN: This is Pete Glassman. I have to admit I'm not an expert in the area, so I would have to defer to others.
DR. KELMAN: This is Jeff Kelman again. I don't suppose you could address the question of paying for non-performance, patent tickets, inhibiting generics yet on the market, the use of authorized generics to discourage the first six months, and exclusivity problems. All of those might be helpful in increasing the generic dispensing rate and generic substitution rate; particularly pay-for-delay.
MS. TOUFANIAN: Thank you, Jeff. This is Maryll Toufanian. I want to note that your interest in those three topics is definitely noted. I appreciate the comment.

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DR. KELMAN: Thank you.
DR. LAMER: This is Chris. I have nothing to recommend off the top of my head.
MS. NGUYEN: Thank you. Are there other questions from the FDA panel?
(No response.)
MS. NGUYEN: Great. Then I'd like to thank Jeff, Pete, and Chris for their time and move to the next part of the public meeting, which will be remarks from David Gaugh from the Association for Accessible Medicines.
Presentation - David Gaugh
MR. GAUGH: Thank you, Martha, and thank you, panel, for this opportunity to speak today. As Martha said, I'm David Gaugh. I'm the senior vice president of Sciences and Regulatory Affairs at the Association for Accessible Medicines, more broadly known as AAM. Today I'm speaking collectively on behalf of the industry representatives that will be engaging in the upcoming GDUFA III negotiations with the agency.
The generic industry negotiating team is

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made up of three trade associations, the Bulk Pharmaceuticals Task Force, representing manufacturers of active pharmaceutical ingredients, their intermediates, and the excipient sector; the Pharma &Biopharma Outsourcing Association, representing contract manufacturers and the contract development and manufacturing sectors; and AAM, representing the manufacturers and distributors of bulk active pharmaceutical chemicals and finished generic pharmaceutical products and supplies, and other goods and services for the generic sector.
Generic medicines represent greater than 90 percent of all prescriptions dispensed annually in the U.S., but only account for 22 percent of annual expenditures on prescription drugs. This translates into producing over 70 billion doses of generic medicines annually in the U.S. alone, providing more than 3600 jobs at nearly 150 manufacturing facilities; again, that's U.S. alone. Savings to consumers, healthcare systems, and to the federal government are running around

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293 billion, and that's in 2018.
Our members enable patients to have continued access to affordable quality medicines. What other industry can provide this level of savings for America's patients? And indeed, generic medicines provide an unbeatable value proposition.
The first iteration of the Generic Drug User Fee Amendment was enacted on October 1, 2012. The overarching goal of GDUFA was to accelerate timely access to safe and effective generic medicines for the public by providing the agency with supplemental resources by way of the user fees.
In turn, the agency made commitments to achieving agreed-upon regulatory milestones that provided industry with more predictability and certainty as to when the agency's actions would occur during the ANDA review process.
We are currently midway through the first reauthorization period, or GDUFA II, which is due to sunset at midnight on September 30, 2022. We would like to acknowledge the agency's efforts and

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successes in standing up a more modern program to support the review and approval of generic medicines.
This brings us to the reason for today's public meeting. The industry and the agency will soon embark upon negotiations for the second reauthorization of GDUFA, or as we know, GDUFA III. As the industry team works together to collectively represent the generic industry in these negotiations, we believe we share a common goal with the agency; that being enhancing the current processes and improving on what we have built together over the last nine years.
In order to further increase efficiencies and to facilitate timely access to safe, effective, and high-quality, and therefore more affordable, generic medicines, we need to continue to address ways of improving the first-cycle approval rate, further enhancing communications and transparency and refining existing processes to ensure GDUFA III builds upon the lessons learned from the prior authorizations. This will continue to make the

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program robust and successful for both industry and the FDA.
This said, we need to also be mindful of containing the costs of the overall program to ensure that the user-fee program does not create a barrier to entry into the generic space. The industry and negotiating team look forward to working with the agency to continuously improve the generic drug user-fee program, and we thank the agency for the opportunity to share our thoughts today. Thank you.
Clarifying Questions from the Panel
MS. NGUYEN: Thank you, David.
Now, I invite the FDA panel, if anyone has questions.
Alonza has a question.
MR. SHERWOOD: Hello. This is Ted Sherwood with a similar question to AAM. Thank you very much for your summary of the industry and how valuable generic drugs are. As we look again to restart negotiations for a new round, are there factors beyond review and research goals that we

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should be looking at?
MR. GAUGH: Great question, Ted. Thank you. As I said in my opening remarks, we are three associations that are developing the negotiating process for industry. Our three associations, of course, are made up of our own member companies. We are in the process right now, as you know, through the data call process and also through building our priorities; so at the present, I really don't have any specifics I can give you, but we are working to get that information pulled together in the coming weeks and get that information to the FDA.
MR. SHERWOOD: Thank you.
MR. CRUSE: Good morning. This is Alonza Cruse, ORA, director of Office of Pharmaceutical Quality. Thank you for your comments, David. I have a question. You were providing information U.S. based. What is your forecast or anything you can share with the foreign-based generic industry?
MR. GAUGH: Thank you, Alonza. That's a great question, and I wish I could answer right

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here and right now, but unfortunately can't. We are trying to pull that data together. And as you probably well know, while we know where facilities are located, we don't know the volumes of products coming out of those facilities, whether it be API, or finished dose, or packaging for that matter. That obviously is one of the tenets of the CARES Act, to be able to provide that information.

So we are working diligently as an industry, and all three of our associations as an industry, to be able to prepare ourselves for the September time frame when we will start reporting these data to the FDA, but at this point in time, we just don't have that information available to us.

MR. CRUSE: Thank you, David.

MS. NGUYEN: Jacqueline, I think you have a question.

DR. CORRIGAN-CURAY: Sure. Thank you, David, for joining us today and for those remarks. I wanted to just maybe ask you to expand. You talked a little bit about building upon the successes, so I understand there may be room for

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improvement. But where do you think the GDUFA program has been particularly successful and of benefit? Maybe you could highlight the areas that you think are working very well.

MR. GAUGH: So when we look at going from GDUFA I to GDUFA II, we learned many, many lessons, for those of you that were in GDUFA I, from that process and those processes, and of course negotiated a lot of that information into GDUFA II. We got a lot of successes in there. As I had mentioned, the communications and transparency has much improved GDUFA II over GDUFA I.

We still feel there are areas of further improvement, and I believe Maryll and others addressed that this morning as well, so we want to go down that path.

We also think working collaboratively and collectively together, FDA and industry, we can work to get the first-cycle reviews in a better place. They have gone from a point in early GDUFA I at about a 9 percent first-cycle review period, so now we're upwards of the mid 20, 25-ish percent

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for that first-cycle review, but that's not nearly where we need to be for both industry and the FDA to be as efficient as possible. So I think those are two areas we could really look into.

Oh, and just to add to that one more, and Rob Lionberger of course addressed that, but the complex products, we've got additional information in GDUFA II, or opportunities I should say, and processes in GDUFA II for the complex products. We need to take that potentially to the next step in GDUFA III. I'll stop there.

DR. CORRIGAN-CURAY: Great. Thank you so much.

MS. NGUYEN: Thanks, David.

Are there any other questions from the FDA panel?

(No response.)

MS. NGUYEN: If not, this concludes the morning portion of the public meeting. We will resume this afternoon at 1:00 p.m. Eastern Standard Time, when we will begin with presentations from healthcare providers and other stakeholders and

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proceed to the open public comment period.

Thank you to all of the presenters and participants. We will see you at 1 o'clock.

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

AFTERNOON SESSION
(1:00 p.m.)

MS. NGUYEN: Good afternoon, and welcome back to FDA's virtual public meeting on the Reauthorization of the Generic Drug User Fee Amendments of 2017 or GDUFA. My name is Martha Nguyen, and I am the director of the Division of Policy Development in OGD, and I'm the moderator for this meeting.

This morning we heard from officials from FDA, other government agencies, and trade associations. This afternoon we will have presentations by healthcare providers and other stakeholders, as well as an open public comment period. Finally, Jacqueline Corrigan-Curay, the director of the Office of Medical Policy in CDER, will make closing remarks and adjourn this public meeting.

First up, I would like to introduce Jillanne Schulte Wall, who is from the American Society of Health-System Pharmacists. She does not have slides and will be making remarks only, so you will

see a slide that does not advance during her presentation.

Presentation - Jillanne Schulte Wall

MS. SCHULTE WALL: Thanks, Martha.

Good afternoon, everyone. My name is Jillanne Schulte Wall, and I'm ASHP's senior director of Health and Regulatory Policy. On behalf of our 55,000 pharmacists, pharmacy students, and pharmacy technician members providing care in acute and ambulatory settings, we thank FDA for your work implementing the GDUFA II priority, and we look forward to continuing to work with FDA and other industry stakeholders on the development of a strong GDUFA III.

ASHP believes that the allocation of sufficient federal resources to the FDA to meet its mission is a necessity, and that those funds should come primarily from federal appropriations. We strongly support increased appropriations for FDA, and we work cooperatively with a line for a stronger FDA to advance that cause.

While drug user fees do not replace the need

for increased appropriations, they now play an essential role in the drug ecosystem. GDUFA and GDUFA II have helped speed the approval process and bring safe and effective generic drugs to market. We anticipate that GDUFA III will build on that foundation.

As everyone in this meeting knows, FDA's public health mission has never been more critical than it is at this moment. Our members have looked at the agency for strong guidance and assistance during the COVID-19 response and they received it. However, the pandemic has also laid bare the limitations of our drug supply chain, and we believe GDUFA III presents an opportunity to work collaboratively on new initiatives that strengthen the entire supply chain from R&D to approvals, to hospitals and health systems, and the consumer.

I'd like to highlight three areas that ASHP would like to see included as GDUFA III initiatives: [indiscernible], shortages, and supply chain strength. I'd like to note here that nothing that ASHP is positing as an option for an

initiative moving forward is meant to cast an aspersion on anything anyone has currently done. We just think that we're at an inflection point where we could theoretically use GDUFA III as a jumping-off point to meet some of the policy priorities that have been long standing and that have really been keyed up by the pandemic.

ASHP has long-standing professional policy that supports legislation and regulations that promote increased patient access to less expensive generic drug products. ASHP policy emphasizes that safety comes first and the desire to rush drugs to market should never surpass the need to ensure products are safe and effective. We are pleased to see an increase in the number of generic drug approvals, more choice, and more competition benefit for patients.

That said, our members have been concerned about the recent state of quality issues and some of the very quick approvals we've seen during the pandemic, and we recognize that some of those are EUAs, but at the same time we wanted to highlight

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this for both industry and FDA, that there's been some concern amongst the FDA and the very close FDA watchers about the speed of approvals and also some of the quality issues we've seen with some of the manufacturers. We have no doubt that manufacturers want to produce high-quality generic drugs and that FDA wants to approve only safe products. We'd like to see resources dedicated to initiatives like continuous quality improvement to help everyone reach these goals.

Quality has also played a role in drug shortages. Since GDUFA II, we've continued to see manufacturing issues contribute to shortages, and this has been true for both generic and brand products. However, on the generic side, we've also seen products exit the market because of these manufacturing difficulties and the cost of production versus a relatively low product price.

These shortages hit fever pitch following Hurricane Maria when we were dealing with shortages of everything from sterile injectables to sterile saline. Similar pressures have arisen around

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supportive medications needed to treat COVID-19 patients. While we were pleased that the CARES Act addressed many of our long-standing policy priorities around shortages, we believe more work remains.

While the FDA may not be able to compel a manufacturer to continue to make a product, it will be important for the agency to continue to prioritize applications for medically necessary products that are in short supply and to use generic drug user fees to enhance FDA efforts to prevent drug shortages. In the same vein, we encourage the agency and stakeholders to consider methods of using GDUFA to shore up our supply chain.

As noted above, the pandemic has highlighted weaknesses in our supply chain, including API sourcing and offshoring of operations. ASHP believes there is no single solution. Simply onshoring all operations still creates vulnerabilities. Although we're talking to Congress about potential policy solutions, we

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encourage FDA and industry stakeholders to consider options for utilizing GDUFA to strength our supply chain.

I just want to note here that ASHP is happy to work with anyone who is interested in these policy priorities. We've done a lot of work on shortages over the past five years, and we will continue that work. We don't want to be in the position of making requests and not offering to assist in getting them done, recognizing that we at the end of the day are not the ones who pay the user fees.

We cannot overstate the importance of generic drugs to our healthcare system. Generic drugs carry the promise of significant savings over their branding counterparts. Over the last decade, they've saved our healthcare system trillions of dollars, however, we continue to see generic prices kick up and skyrocket in some cases.

Everyone in this meeting is aware of these issues, so I won't belabor the point, but suffice it to say that massive inexplicable price

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fluctuations hurt our patients. At the same time, we also recognize that pricing certain drugs too low has pushed products off the market. This is true for many of the first-line antibiotics, and it has also inhibited the development of new generic products that are relatively inexpensive.

ASHP has been engaged in discussions with policymakers about balancing the need to protect patients from huge price spikes and incentivizing new products. We have been engaged with Congress and others, but believe that the FDA should explore ways in which to examine and study these trends using GDUFA resources.

Although drug pricing is generally out of the scope of FDA's purview, we believe that FDA is uniquely situated to discuss responsible pricing decisions with manufacturers during the application process.

Thank you for the opportunity to present our little wish list for GDUFA III. We recognize that FDA has limited authority in some of these areas and that there are a number of competing priorities

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for GDUFA funds, but we urge strong consideration in the initiatives we outlined. At the end of the day, we believe that many of these areas would be mutually beneficial for all stakeholders. Thank you so much.

MS. NGUYEN: Thank you, Jillanne.

Our next speaker is Tony Barrueta from Kaiser Permanente.

Presentation - Anthony Barrueta

MR. BARRUETA: Thanks, Megan [sic]. It's nice to follow John's very excellent testimony. Thank you for the opportunity to testify today. I'm Tony Barrueta, senior vice president for Government Relations with Kaiser Permanente.

As the largest private integrated healthcare system in the United States, we provide pharmacy benefits and services to over 12 million people. Our model combines coverage and care delivery, and we operate pharmacies that dispense drugs prescribed by are Permanente Medical Group physicians.

Our mission for pharmacy, like all of the

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services we provide, is to deliver high-quality, affordable care and to improve the health of our members and the communities we serve. Kaiser Permanente appreciates the opportunity to provide feedback on GDUFA II, and we strongly support FDA and the generic industries' efforts to strengthen and improve the program with GDUFA III.

In my remarks today, I'll provide some background on why generic drugs are so important to Kaiser Permanente's ability to provide high-quality, affordable pharmaceutical care. I'll also identify three broad issues KP hopes FDA, the generics industry, and Congress will together address during the upcoming user-fee negotiation and reauthorization: 1) reducing barriers to generic competition; 2) improvements to quality and safety oversight; and 3) mitigating prescription drug shortages.

Kaiser Permanente has long been an industry leader in generic utilization. More than 91 percent of the drugs prescribed in our system are generic. That exceeds the very high market

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averages of 89 percent, which just indicates how central and critical generic drugs are to the American healthcare system.

Our evidence-based approach to designing pharmacy benefits helps facilitate competition among drugs. Our pharmacists and Permanente Medical Group physicians collaborate closely to develop our formularies. When generics perform just as well as or better than a more expensive brand drug, they prevail within Kaiser Permanente. Every one-tenth of 1 percent increase in generic utilization saves our system $28 million. These savings help us invest in care and quality initiatives that benefit our members.

We're working hard to extend that commitment to generic drugs onto biosimilars as well. While others have been slower in transitioning to biosimilars, Kaiser Permanente has embraced them from the beginning. We adopted the first FDA-approved biosimilar, Zarxio, and now use it instead of Neupogen in approximately 95 percent of cases. We replicated the success with Inflectra,

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which we use more than 80 percent of the time instead of the originator Remicade.

In the rest of the market, Inflectra and Zarxio utilization hover around 3 and 32 percent, respectively. In late 2019 and early 2020, we've launched new initiatives to adopt three additional biosimilars, Truxima, Kanjinti, and Mvasi. Our adoption rates already exceed 90 percent for each of these products.

A few words on competition more generally, generic drugs have resulted in substantial savings for patients, taxpayers, and the entire healthcare system. The Association for Accessible Medicines estimates that generics and biosimilars have saved the United States healthcare system almost $300 billion in 2018 and as much as $2 trillion over the last decade. These savings help deliver on the benefits promised to society in exchange for the government-granted intellectual property rights such as patents and market exclusivities that protect monopoly pricing power on branded drugs.

The GDUFA program is essential to

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facilitating increased generic market entry and making the overall pharmaceutical market more competitive. GDUFA I and II made significant strides in addressing the ANDA backlog, helping bring more competition to market faster. At the time of the GDUFA I's enactment, FDA's backlog was over 2800 ANDAs.

Today the backlog has effectively been cleared, and FDA is approving record numbers of generic drugs. In fiscal 2019, the agency approved nearly 1200 generic drugs, and all-time high. This is a major accomplishment and will help provide more affordable pharmaceutical care to patients over the long term. We applaud FDA and the generic industry's strong partnership and commitment to addressing this challenge.

Despite considerable progress over the last 10 years, there is still more work to be done to make the market for prescription drugs competitive. Many recently approved generics are not available to patients due to abusive tactics used by the branded pharmaceutical industry to delay and

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prevent competition.

As of 2019, 43 percent of generics approved since 2017 were not on the market. Out of 69 branded drugs expected to lose market exclusivity between 2010 and 2016, competition was delayed for 29 percent of generics and never occurred for 16 generics.

Patent litigation was the most common cause of delays. Anticompetitive abusive patents can significantly delay generic and biosimilar availability, hampering our ability to provide more affordable options to Kaiser Permanente's members. It also creates uncertainty that disrupts their ability to design optimal pharmacy benefits.

Kaiser Permanente would support inclusion of policies that will help address these abuses in the next user-fee reauthorization package. We strongly support the steps FDA has already taken to collaborate with the Federal Trade Commission and curb abuses of citizen petitions and REMS.

Common-sense changes to the Orange Book could help build upon those steps. Brand name

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manufacturers often obtain numerous patents and list them strategically in the Orange Book to interfere with generic manufacturers' attempts to bring products to market under the Hatch-Waxman framework. Policy changes that would require FDA to promptly remove patents, invalidated by the patent trial and appeal board from the Orange Book, would help mitigate these abuses.

GDUFA user fees also help to fund important quality and safety initiatives, including FDA inspections of foreign and domestic manufacturing sites. Drug quality and safety is of the utmost importance to Kaiser Permanente. We support FDA's efforts to ensure all drugs are manufactured to the highest standards, however, recent high-profile incidents have shaken consumer confidence in generic drug integrity and identify potential areas of improvement for the GDUFA program.

For example, investigations found that foreign manufacturing sites in India were fraudulently manipulating quality data and successfully hiding substandard conditions from

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inspectors. In the past few years, some widely used drugs relied on by many of our members, like Zantac and metformin, have also been recalled over concerns about NDMA contamination, as you've heard, of probable human carcinogen.

Under FDA's current quality framework, manufacturers are typically responsible for assessing chemical quality of their medications and self-report the results to FDA. Inspections are the agency's primary means of independent quality oversight. Direct testing of drugs by the FDA for quality and safety is limited.

The majority of manufacturing also takes place in foreign countries where FDA's ability to conduct robust inspections has been limited. While domestic inspections are usually unannounced, most inspections of foreign facilities are announced 12 weeks in advance giving manufacturers time to conceal potential deficiencies. Despite growing concerns, FDA is also conducting fewer inspections overall due in large part to trouble recruiting and training inspectors. FDA commendably acknowledges

these challenges, noting inspections are not always a reliable predictor of quality.

Safety is one of the core components of FDA's public health mission, therefore, Kaiser Permanente strongly encourages FDA to take steps to improve quality and safety oversight in GDUFA III in the next user-fee authorization. Stakeholders across the healthcare system are relying on FDA and the industry to get this right.

Specifically, we would support increasing resources for FDA to hire and train inspectors; requiring unannounced inspections of foreign facilities; giving FDA more resources to engage in direct chemical testing of drugs; and establishing a framework to develop reliable and transparent quality ratings for the manufacturing sites used to make different products based on FDA inspections or reviews from independent third parties.

Drug shortages remain a persistent problem in the pharmaceutical market. Shortages can occur for many reasons, including appropriate regulatory actions, lack of economic incentives, manufacturer

imposed limitations, trouble accessing raw materials, and demand exceeding supply.

The COVID-19 pandemic has also exacerbated risks of shortages and further exposed national security vulnerabilities in this area. Shortages resulting from export bans, slowdowns of API manufacturing abroad, panic buying, and runs on potential COVID-19 therapies are likely to continue and could be difficult to predict and plan for.

Regardless of what drives a shortage, they often leave providers and patients scrambling to identify safe alternatives for treatment. This could lead to suboptimal health outcomes when care is delayed or alternative treatments are not as effective or well tolerated.

Some studies also estimate that shortages cost hospitals hundreds of millions of dollars a year. These costs are attributable to dedicating staff time to finding alternatives, having to purchase from vendors outside our usual supply chains at higher prices, and price increases by remaining manufacturers aftermarket exits. I can

tell you that all of these issues are major issues for our pharmacy team working to make sure we have consistent access to prescription drugs.

As an integrated system, Kaiser Permanente has some advantages with respect to our ability to plan for and manage drug shortages. We're able to strategize and communicate critical information across pharmacies, hospitals, and clinicians across our system.

We work to mitigate shortages by proactively surveilling market conditions and warehousing ample supplies of core formulary generics. Our drug information team proactively works to identify alternatives for drugs under threat of shortage and puts together memos to educate clinicians about what is happening.

We also evaluate our vendors' manufacturing competencies and their ability to deliver needed supplies when possible. We sometimes use longer term contracts to support consistency and forecast predictability. We also sometimes will penalize manufacturers for failure to supply to help offset

costs of having to use another vendor.

Nevertheless, we are not immune from the effects of drug shortages. Over the years, we've experienced shortages on a range of drugs likely attributable to many different causes. For example, we've experienced shortages of local anesthetics, sodium chloride injection, epinephrine auto-injectors, and several other generic drugs such as diphenhydramine injection. We've also seen shortages of injectable opioids, small volume bags of IV fluids, sterile injectables, and antibiotics.

When we can anticipate shortages, we can better execute strategies to help build and conserve supply to safeguard against disruptions and care. However, the reasons for shortages are not always disclosed by manufacturers. There's also very little reporting on API shortages and oversight of manufacturers plans to prevent shortages.

Kaiser Permanente therefore strongly supported provisions in the CARES Act that bolstered FDA's drug shortage reporting framework

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by extending reporting requirements to API and requiring manufacturers to maintain risk management plans. We hope FDA and Congress will build on these provisions to ensure manufacturers operationalize appropriately robust risk management plans.

We also support the work of FDA's drug shortage task force to better characterize shortages, improve data sharing, and ensure robust and accurate reporting by manufacturers. We're hopeful that this information will lead to effective policy solutions to prevent and mitigate more shortages down the road.

I really want to thank you for considering our perspective on all of these important issues. Kaiser Permanente shares in the objectives of the GDUFA program and looks forward to working with the FDA and the generic industry to advance meaningful policies and improvements as part of the 2022 user-fee reauthorization. Thank you very much.

Clarifying Questions from the Panel

MS. NGUYEN: Thank you, Tony.

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Now I'd like to ask our FDA panel if they have questions for Jillanne or Tony. I think Maryll has a question first.

MS. TOUFANIAN: I do.

Tony, Thank you very much for your comment, and I appreciate the specificity of the detail with respect to drug shortages and quality and safety surveillance considerations. I do have one question for last request, and that is that you indicated Kaiser had some specific questions related to the FDA's activities in patent listings and in the Orange Book, and I would request, either here or in a submission to the currently open public docket regarding patent listings, that you provide some additional specificity for what would be useful from your entity's perspective in that regard.

MR. BARRUETA: Thank you. I don't think we have yet submitted comments to that docket, but we would be very happy to do so. We're happy to take that down that path.

MS. TOUFANIAN: Thank you.

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MS. NGUYEN: Other questions from the panel?

MS. BOAM: Hi, Martha. This is Ashley Boam. I have a question for Jillanne. I was wondering if you had any specific suggestions in the quality space. You talked about a desire to see more to improve in the quality space, and I would be interested if you had any specific suggestions you'd like to share with us today.

MS. SCHULTE WALL: Yes. Actually, we do have specific suggestions, and some of them kind of mirror what Tony brought up, so things like increased funding for inspectors. We are really interested in continuous improvement processes, and that's an area that my colleague, Mike Gania, really specializes in, so he'd be the one to really provide some of the detail there. But we're happy to submit comments to the docket with much more detail than what was included in my very generalized remarks.

MS. BOAM: Thank you so much.

MS. NGUYEN: Alonza, did you have a question?

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MR. CRUSE: Good afternoon. This is Alonza Cruse. I have a question for Tony Barrueta, and maybe a question, more a comment. First of all, I want to just thank you for your comments that you raised surrounding the foreign inspection piece. As you know, they certainly represent a unique logistical and coordination challenge in that space.

Did you have any other specific recommendations in the work that is done on FDA inspections in an international space that you can either share here?

MR. BARRUETA: It's a very good question, and I guess I would acknowledge the challenges in setting up a system to do this appropriately. As a major purchaser of drugs, we do our best to make sure that on our end we're able to validate the capabilities of suppliers overseas, and I know that that's true for everyone in the industry.

I think that there is a need -- it may be appropriate, Alonza, for the FDA to work with purchasers more directly, to think about how we

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might develop a more coherent surveillance system to identify gaps, knowing that it's going to be impossible -- I think it would be impossible to have as robust a global surveillance safety system as we do in the United States, but I do think there's a lot that we could do together to try to improve that.

At the end of the day, it's really important to purchasers that the regulator we rely on, to make sure that safety does exist in the FDA, has the appropriate resources and reach to do this. I don't think we can actually rely on voluntary private efforts in this space, and it's something that both FDA and Congress should ensure is adequately resourced to enable it to happen; because as I think Jillanne mentioned, it's really unlikely that we can onshore all of the manufacturing as some people would like.

We will always have to have a global pharmaceutical supply chain, and we need to have a regulatory structure that is appropriately financed and appropriately designed to make that safer and

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safer.

So I don't have a specific rifle-shot solution to this. I basically think we need to take this on as a complex, comprehensive matter that needs to be addressed by the regulatory agency that's responsible and for all of the purchasers who are reliant upon that.

MR. CRUSE: Thank you for that feedback.

MS. NGUYEN: Any other questions from the FDA panel for Jillanne or Tony?

(No response.)

MS. NGUYEN: If not, I'd like to thank you for your time and move on to the next portion of the meeting, which will be presentations from other stakeholders.

MR. BARRUETA: Thank you.

MS. NGUYEN: Thank you.

The next presentation will be from Scott Tomsky, who is from Teva Pharmaceuticals.

Presentation - Scott Tomsky

MR. TOMSKY: Thank you, Martha.

Good afternoon, and thank you for the

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opportunity to speak today as we get set to embark on the second reauthorization of GDUFA. My name is Scott Tomsky. I am vice president of Regulatory Affairs, Generics, North America at Teva. I've been engaged with GDUFA from the beginning. I worked to implement GDUFA I, I was a member of the GDUFA II negotiating team, I am an active member of the industry implementation team for GDUFA II, and I'm excited to be a member of the industry team for GDUFA III negotiations set to embark later this year.

At any point in time, Teva has on average over 200 ANDAs at various stages of review with FDA. Teva's perspective reflects our repetitive interactions with FDA across many applications. As we have already heard today, FDA has made major strides in standing up a more robust, predictable, transparent, and scientifically driven system to support the review and approval of generic drugs.

While Teva applauds the agency's efforts to date, we still see significant areas for improvement. Given the importance of generic drugs

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to patients, the healthcare System, the U.S. economy, we believe FDA needs to continue to evolve and strive for greater efficiency, predictability, and regulatory flexibility for the review and approval of generic medicines.

One way to help bring these products to market more efficiently so that patients can benefit from access to lower cost alternatives to pricey medications is to further build a GDUFA infrastructure that further supports the review and timely approval of more complex ANDAs.

As we look back at the successes we have achieved in GDUFA II, and as we look ahead to the possibilities of GDUFA III, Teva believes that a greater focus on regulatory flexibility and transparency are of paramount importance. As I would detail in my remarks today, FDA must examine its practices in developing robust regulatory science to underpin a more flexible and innovative approach to generic drug review.

During the last eight years of GDUFA II, FDA cleared the ANDA backlog, issued hundreds of

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product-specific guidances, increased the number of first-cycle approvals, created a formal pre-ANDA meeting process, and clarified many of its policies through issuance of guidances for industry.

In GDUFA III, FDA needs to take additional steps to increase the number of first-cycle approvals, especially for complex generics. FDA should examine its practices that may be impeding generic entry such as the rigid adherence to product-specific guidances and qualitative/ quantitative similarity, as well as creating a more tailored review process to support product approvals.

To start, I want to thank FDA for its willingness to work with industry on reducing the number of ANDAs that are RTR'd. Industry raised those issues with you during GDUFA II implementation, and fewer ANDAs are being refused receipt for trivial reasons. If the agency can show similar flexibility in a few of the areas I will highlight in my remarks today, I believe it will make an enormous difference for the generic

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industry.

One of the biggest challenges Teva still encounters with FDA is regulatory uncertainty and unpredictability. This has a tremendous impact on Teva's forecast and business decisions related to planning for launch as well as product selection.

Sometimes regulatory delays and lack of transparency are so challenging and insurmountable that Teva will choose to abandon an ANDA rather than trying to get it approved and launched, or we may forego development of a project because of the uncertainty around the approval path and timeline.

When we are unsure of FDA's timeline in acting on an application or what action FDA will take due to lack of clear regulatory policy or guidance, it makes it nearly impossible to decide to scale up our manufacturing process and prepare to launch the product. It is often more cost effective for Teva to abandon a project rather than throw manufactured product away due to delays and launch timeliness stemming from FDA delays. The impact of FDA's lack of regulatory predictability,

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transparency, consistency, and flexibility is felt most acutely for our applications for more complex generic products.

As noted in a 2019 report by the Government Accountability Office, the average rate of first-cycle approvals overall was 12 percent with most applications taking up these three review cycles to reach approval. Additionally, GAO notes that complex drugs are highly unlikely to be approved in the first cycle. For some routes of administration commonly associated with complex formulations, the first-cycle approval rate noted by the GAO was zero. This is consistent with Teva's experience as well.

But why is it this way, and does it have to be? Complex generics may be more akin to their new drug counterparts in the type of review required. It's notable that FDA's Office of New Drugs is able to approve over 90 percent of applications, even for new molecular entities, on the first round of review.

Now granted, PDUFA is structured and

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financed very differently than GDUFA, however, we have to dig in closer and take some lessons to be learned in the way FDA works with new drug sponsors to ensure that applications are in shape to be approved when they are submitted to the agency.

For example, we should consider setting goal dates from the date of filing and not from the date of submission for complex generic applications as is done in PDUFA for new molecular entities and BLAs, which provide the agency a bit more time to do a substantive review.

Teva has also envisioned a different review goal structure for GDUFA III, where complex generics are reviewed under different metrics and where OGD's review completion target is lowered to 75 percent rather than 90 percent today. This would allow the Office of Generic Drugs the flexibility to miss a goal date when they feel they can work toward an approval, but it can only work if sponsors have more insight into the review process and confidence and clarity to where an application review stands if a goal date is missed.

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The application cannot fall into oblivion as often is the case today when a goal date is missed.

One of the best results of GDUFA II was the creation of the pre-ANDA review process, which somewhat reflects the new drug model. Industry pushed hard to gain more FDA feedback prior to ANDA submission, and the agency has delivered on that commitment. Teva specifically has found the product development meeting to be very useful and an important tool for complex products.

FDA puts a lot of time and effort into preliminary responses and into the meeting discussion, and we would love to see even more of that kind of collaboration in GDUFA III. Teva feels that can bring more collaboration to other areas of the ANDA review process and reap similar benefits.

First, mid-cycle review meetings, they're currently a lost opportunity from Teva's prospective. This meeting opportunity borne out of GDUFA II was an encouraging avenue for industry submitting complex generic drug products, however,

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it has been nothing close to what was envisioned or discussed. Teva has experienced several of these mid-cycle review meetings and have found them to be of poor use of FDA and industry resources, as well as a lost opportunity to reduce the likelihood or need for a subsequent review cycle.

The intention of these meetings coming out of GDUFA II was to create an avenue where the review team and the applicant would discuss the initial review deficiency and clarify any questions that may require further discussion. This would ensure that the sponsor understood what was being asked, as well as clearly understanding the agency's expectations to address the comment fully. Rather, these meetings have been unfruitful and simply results in FDA communicating that a deficiency letter was issued on a particular date and that the response is due on that particular date without an opportunity for discussion between the review team and the applicant.

In regard to complete response letters, FDA relies too heavily on them today and should look

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for more opportunities to complete a review with no further questions during a review cycle, and the result of FDA's proclivity to default to major CRLs is a significant lag in the generic product's breach in the market.

A more interactive review process may reduce the number of overall CRLs, especially major CRLs. Wherever possible, information requests should be used in place of a minor CRL, which in turn should be used in place of major CRLs. Using information requests more effectively throughout the review cycle could address issues that are being punted to CRLs today.

FDA has also implemented a policy of not using information requests or discipline review letters after a GDUFA goal date has passed, which leaves the agency no choice but to issue a complete response letter when the answer to an IR or CRL could have led to an approval.

After FDA issues a CRL, currently sponsors our only able to follow up with clarifying questions. There needs to be a process for

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sponsors to have post-CRL meetings for more in-depth discussions as there are for new drugs. This type of meeting likely would be most useful for complex drug products and could be piloted for those products first.

Another practice that FDA should re-examine under GDUFA III is the agency's policy to apply revised product-specific guidances to pending ANDAs. Practically speaking, FDA requires applicants to meet new and revised guidances even after applications are submitted or tentatively approve. This event occurs routinely, even as FDA reminds us that guidances are not binding. This is especially egregious because FDA does not go back and ask approved ANDAs to meet new product-specific guidances, thus treating similarly situated parties completely differently.

If FDA would not ask approved applicants to meet a new guidance, then they should not do so for pending ANDAs. Every time industry has to redo a study, it delays generic entry and adds to the cost of products to the patients. In most cases, FDA's

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revisions to product-specific guidances may improve bioequivalence testing methodology, but they don't impose changes that are critical for demonstrating bioequivalence to the reference-listed drug. If the changes were made because previously approved ANDAs had been determined not to be bioequivalent, it would be appropriate to hold pending and approved ANDAs to the same standard.

I also think it's important to note that FDA does not just do this for pending ANDAs but also for ANDAs that the agency has already tentatively approved. Were it not for blocking patents or exclusivities, a tentatively approved ANDA would be approved, and yet FDA does not require approved ANDAs to meet the same revised bioequivalence recommendations. You can see how this result appears to be absurd.

Another area to be addressed is the presubmission facility correspondence or PFC. FDA currently is not using the PFC process effectively, nor in the way it was contemplated and discussed during GDUFA II negotiations. This was a promising

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idea under GDUFA II that could have provided more opportunities to reduce review time from 10 months to 8 months for priority ANDAs.

During GDUFA II negotiations, industry agreed to provide a listing of facilities referenced and to be used in a particular ANDA similar to information that's included on a basic 356h form for PFC. Subsequently, FDA issued guidance that essentially requires the submission of a mini ANDA for a PFC.

This is an overly burdensome process that contravenes the purpose for which the PFC was created, namely to identify all facilities and permit FDA a 2-month lead time to assess and plan if an inspection was determined to be necessary. This would in turn provide an opportunity to expedite review and approval priority ANDAs that submit their facility information two months ahead of a planned ANDA submission date.

FDA needs to re-examine the PFC process to bring it in alignment with the original intention and allow sponsors that are diligent in submitting

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facility information for priority products in advance to avail themselves and opportunity to a pathway.

Finally, I would be remiss if I did not mention today the impact of FDA's regulatory approach for my commercial colleagues. While brand name products receive an outsized amount of attention related to their pricing and marketing, we should not shortchange the effort it takes to bring a generic product to the market.

My commercial colleagues walk a tightrope of profitability, which is made even more treacherous by the constantly shifting winds of FDA regulation for generic medicines. When we don't know what is going to happen with FDA, it's bad for business.

One great example here is timing of approval actions. Applications from multiple sponsors are at times submitted on the same day and are likely to be approved at the same time. We have had ANDAs where FDA approved our application a full day or several days later than other applications because we had a different project manager or because there

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were administrative issues with an ANDA. This has a major impact on business, which can sometimes make it significantly more challenging to launch products because others are out ahead of us.

We often hear FDA asking why the number of launches doesn't correlate with the number of approvals. When the FDA approval process drags on or becomes too unpredictable to support the business case, products won't launch. It's that simple. The truth of the matter is that the risk factors of regulatory uncertainty can make a launch unviable. Even when FDA eventually approves a product, the business case may no longer be there to support a successful launch, and we conclude it's preferable to abandon the project.

For these reasons, I often have difficulty convincing my commercial colleagues to pursue projects for small market drugs that are going to have competitors. It's even one of the pitfalls I noted in my remarks today that occurs for an ANDA, or a product like that, that will have wasted the development and manufacturing resources, and

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there's no return on the investment.
I'm looking forward to discussing these and other issues with FDA as the GDUFA III negotiations get underway. If we work together to take steps towards a better, bolder regulation of generic drugs, it will benefit all of us, and even more so the patients that take our medicines every day. Thank you, and I'm happy to answer any questions.
MS. NGUYEN: Thank you, Scott. If you can hang on, we will take questions from the FDA panel after two other presentations from stakeholders.
The next presentation will be from Diana Zuckerman from the National Center for Health Research.
DR. ZUCKERMAN: Thank you so much for the opportunity to speak today. Can you hear me?
MS. NGUYEN: Yes.
Presentation - Diana Zuckerman
DR. ZUCKERMAN: Fantastic.
I apologize in advance for my slides. There were some technical difficulties with downloading them, but I think we'll do pretty well with them

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regardless.
I just want to start out by saying the National Center for Health Research is a non-profit think tank. We focus on the safety and effectiveness of medical and consumer products, and we don't take money from companies that make those products. My particular perspective -- because of my training in epidemiology and public health at Yale, but also a dozen years in the House of Representatives, and the Senate, and at HHS, and at the White House -- comes both from the policy part of the equation as well as the public health part, but I'm going to be focusing on public health today.
As everyone knows, safe and effective from the FDA's point of view means that the benefits outweigh the risks for most patients and, of course, the popularity of generic drugs is based on the assumption that the risks and benefits are essentially the same for generics as they are for brand name drugs, even though we know they're not exactly identical.

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Of course FDA's drug approval criteria are to be safe, to be effective, and also that they be inspected to make sure that they're being made the way they were supposed to be made and not contaminated, and that they're really exactly what they're supposed to be.
For patients, the question is do these drugs work as they're expected to; how sure can patients be that this generic that they're going to take works and is as safe as the label states; and how consistent is the label with the most recent data from postmarket surveillance and other studies that are done outside of the government?
From a public health perspective, as I think about how GDUFA can improve, my big concern is that performance data are currently based on speed as well as meetings with industry, which help move things along more quickly, and I have no concern about that in terms of, yes, we all want safe and effective generic drugs on the market as soon as possible, but performance data should also be based on patient-centered outcomes.

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Yes, generics cost less, generally, sometimes a lot less and sometimes just a little bit less. But cost is not the only issue of importance to patients, and I was really glad to hear Jacqueline Corrigan-Curay mention that this morning. We agree completely.
There is an "H" missing on my slide, but it should be saying, "How can GDUFA improve?" The most important priority for patients is having generic drugs that are safe and effective. So the question for patients is how careful are these FDA reviews? How careful is that scrutiny, and are the resources and is the money from user fees and from appropriations adequate to really prioritize that review in terms of safety and effectiveness, not just speed?
Patients want these inspections to be thorough, and in addition to the reviews, they want the inspections to be thorough, and especially foreign inspections. You've heard something about that earlier in the previous panel, which I was very glad to have been a focus. But I just want to

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say that GDUFA needs to support inspections. It's not clear to me to what extent these user fees are currently used for inspections.

We heard this morning that in some cases I guess inspections were stopped because of the pandemic. The foreign inspections apparently are still postponed because of the pandemic, and this is something that absolutely needs to be resolved as soon as possible.

We understand all the limitations, and we certainly want inspectors to be in a safe situation, whether its domestic or foreign inspections, but we can't continue to have no inspections. Even of course before the pandemic, there were problems with not enough inspections. We also agree that there's a problem when companies are told weeks in advance that there's going to be an inspection rather than having a date by surprise.

Well, I don't know what your slide looks like, but when I look at it, all the D's are missing. How can GDUFA improve the information

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available to patients and providers? In addition to premarket -- and of course the premarket stage is really most important and the scrutiny at the premarket stage is most important, but we also wanted to make sure that GDUFA is adequately supporting postmarket surveillance.

I don't have public information about how much GDUFA fees are used for postmarket surveillance. I know that PDUFA does support postmarket surveillance and that MDUFA does not support postmarket surveillance. So we hope that GDUFA is supporting postmarket surveillance, but not just supporting it, but adequately supporting it. In addition to the traditional kind of postmarket surveillance, GDUFA should also be providing support for FDA staff to create things like patient-informed consent checklists when those are needed to help out with medical guides.

I just want to actually give a personal experience here. I'm currently taking two generic drugs, and I have found that the medication guides that come with these drugs are sometimes including

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information that's either inaccurate or confusing. In fact, I even called Teva about one that I was taking because I thought that the information was incorrect, but the person I talked to there, despite going up the ladder as much as I could, clearly had no idea what I was talking about.

So the question in my mind is, if the company is not going to be responsive, are there FDA staff that consumers can contact about apparently incorrect or confusing information on medication guides?

In addition to medication guides and something like an informed consent checklist that patients could find, GDUFA should also be supporting Dear Doctor letters and warnings to patients about new information about risks or contraindications.

From our point of view, regardless of whether these Dear Doctor letters or warnings are coming out of the FDA, in which case, of course, FDA staff needs to write them, or whether they're going to be coming out of the companies -- but in

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that case FDA staff should also be working with the companies to make sure that these letters are going out appropriately, that they are understandable and clear, and that they are getting the attention that they deserve.

Postmarket studies are absolutely important, but it always makes me a little nervous to talk about it because I don't want to imply that premarket isn't the most important part of the equation. We don't like it when patients really feel like guinea pigs. There are many different kinds of postmarket studies that can be helpful. The Sentinel program is one. Adverse event reports can be helpful. There are other real-world data that can provide useful information.

As someone trained in epidemiology, I know that claims reports and a lot of the big data that are used by Sentinel and others have a lot of flaws and a lot of confusion about what they actually mean. To some extent, the data can be manipulated to show whatever people want it to show.

So that can be helpful; the real-world data

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can be helpful, but it, in and of itself, isn't enough. Even for postmarket studies, sometimes clinical trials may be needed, especially when it seems that certain products are not as safe or not as effective as we expect that they are, that they should have been.

The bottom line really is, are generics as good as name brand medications, and do patients and consumers have confidence that they are as good? We have seen over the years a certain amount of increased cynicism and concern that they may not be quite as equivalent as we expected or thought.

This morning, we also heard from the commissioner about some of the changes that were made during the pandemic, and we understand the need for urgency during the coronavirus pandemic, but it was certainly worrisome to hear that apparently some supplemental applications were going forward without even being reviewed by the FDA first.

I didn't get all that information in enough detail to know what it means. I only know, for

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example, the big example is that coronavirus diagnostic tests -- which is not a GDUFA issue, but those tests were allowed to be sold for weeks before they were reviewed by the FDA. And even after EUAs were authorized, in some cases the FDA did not have the resources to actually review these coronavirus tests to find out how accurate are they. Are some more accurate than others? What are the false positives? What are the false negatives?

That's a different issue, I understand that, but it's certainly gotten the attention of a lot of public health advocates, and it lowers the confidence in the FDA in general, and it certainly lowers confidence when we know that there are generic medications that are being used to treat coronavirus and COVID-19, and we'd like to know more about how that's being scrutinized by the FDA.

So in conclusion, I just want to say, as I've said, cost and speed are the focus of GDUFA II negotiations between industry and FDA, but it's not the most important thing to patients. You're going

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to hear from some patients this afternoon who I think will have compelling stories about why that is true. There's just, I think, a certain lack of transparency for patients, consumers, and public health advocates.

It seems like, from all the user-fee negotiations, the focus is on transparency between FDA and industry, and we need a lot more transparency between FDA and the public, and industry and FDA and the public. It's, I think, very unfortunate that these negotiations, all of the user-fee negotiations, occur behind closed doors without public health folks, patients, and consumers, and providers there in the room. We do get these opportunities to speak, and we're very grateful for that, but wouldn't it be helpful to have a lot more transparency about what's going on?

Also, let me just say on the FDA website, I think there should be a lot more transparency about how the generic drug process works and what are the mechanisms available for patients, and consumers, and others -- public health folks and policy

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folk -- to better understand what the process is, both for getting generics on the market and for postmarket surveillance and studies. Thank you very much.

MS. NGUYEN: Thank you, Diana.

The last of the stakeholder presentations will be given by Priscilla Zawislak IPEC-Americas.

Presentation - Priscilla Zawislak

MS. ZAWISLAK: Thank you.

Thank you, and good afternoon. I'm representing IPEC-Americas, and we appreciate the opportunity to speak today. IPEC-Americas represents about 50 excipient manufacturers, distributors, and pharmaceutical biopharma companies who support the safe production and use of excipients. These are the points that I would like to cover today.

In terms of the overall performance of the GDUFA program to date, IPEC-Americas appreciates FDA's efforts and the necessary updates completed so far of the inactive ingredient database, the IID, and the addition of maximum daily exposure

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limits. However, we continue to be concerned with data integrity and traceability of changes to records made in the database.

In addition to the current cleanup activities under GDUFA II, improvements are needed to minimize confusion when listings are removed and to resolve data integrity problems that continue to occur. Looking at a way to enhance the efficiency and effectiveness of the generic drug review process, FDA reviewers cannot effectively review submissions if the information in the IID cannot be relied upon. Likewise, formulators cannot rely on the precedents listed in the IID as definitive if there are data integrity issues.

FDA should focus on IID policy and data integrity issues not addressed under GDUFA II. In particular, FDA policy development and alignment are needed between the global substance registration system, the IID, and the nomenclature used. Also with respect to drug quality and advanced manufacturing and complex products, in order to facilitate first-time approvals for

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complex generics, FDA IID policy needs to be developed for listing excipients used in new and emerging dosage forms; for example, combination products, transdermal applications, and excipients in medical devices as just a few examples.

Currently, records in the IID are inconsistent, and there is no FDA policy or guidance available for a generic drug manufacturer to review and evaluate precedents for an excipient relative to these types of dosage forms. Considering the rapid expansion and focus on complex generics, it is critical for FDA to provide clarity and a policy position.

Generic pharmaceutical developers are reluctant to vary from excipient grades listed in the IID for new formulations, and it could be due to either unclear bridging justification requirements, the absence of an established regulatory pathway for the evaluation of novel excipients, which are not new chemical entities, and lack of clarity about how to use the information in the IID.

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We are aware that some FDA reviewers have stated that the drug product formulator should use an excipient with an established safety profile that is present in FDA-approved products of the same route of administration and level of use -- we call this formulation by IID -- rather than accepting a detailed bridging justification that meets the safety requirements of FDA as communicated in FDA's own presentations.

As a result, companies may formulate suboptimal drug products in order to avoid the perceived regulatory risk of using excipients, or levels of them, which may not have precedence of use in an approved drug product via the IID. IPEC-Americas believes that this current approach is a deterrent to generic drug product innovation, impedes the development of generic drugs, is counter to FDA policy of using risk-assessment principles, and does not enhance patient safety.

Since there appear to be differences in awareness and consistency in how bridging justifications are addressed by different

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reviewers, IPEC believes that an excipient safety bridging justification guidance document should be developed that defines requirements for good bridging studies and develop policy and reviewer training for when and how a good bridging study might be used to support an ANDA submission. This would improve the quality of ANDA submissions, help increase first-time approval rates for ANDA submissions, and ultimately improve generic drug quality, more timely availability, and lower costs.

Switching then to our final topic, FDA defines a novel excipient as a material or composition that has not been previously used in an approved drug product in the U.S., meaning that it's not listed in the IID for the intended route and level of administration. Novel excipients can be new chemical entities, or as we would call them NCEs, but they can also be co-processed excipients and existing excipients used for new dosage forms or at higher levels of use, just to name a few.

FDA should differentiate novel excipients that are new chemical entities versus a novel

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excipient based on a slightly higher level of use, a chemical modification, a different route of related route of delivery, et cetera.

IPEC-Americas strongly believes that there are many cases where a novel excipient other than a new chemical entity can be justified based on existing human exposure and bridging justifications. Furthermore, we do not agree with, nor understand, the scientific justification for why an excipient with precedence of use for related route of exposure and having data supporting its safe use would be considered novel.

IPEC-Americas highly recommends that FDA accept ANDA bridging justifications in lieu of a 505(b)(2) to address novel excipient uses other than NCEs. FDA needs to consider this policy change for efficiency and to improve and permit access to better generic drugs.

Allowing for reference of information from related excipients will maximize utilization of available safety studies while minimizing unnecessary sacrifice of animals. This strategy is

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aligned with the Tox21 program, the goal of which is to develop strategies that can be used directly by regulatory agencies to regulate chemicals and reduce our current reliance on animal testing for toxicological assessment.

IPEC requested under GDUFA II, and is still requesting under GDUFA III, that FDA develop and implement an independent, novel excipient review process. This can help minimize the potential that generic companies would formulate suboptimal drug products in order to use ingredients only listed in the IID instead of formulating an optimal drug product by using excipients that may not already have a precedence of use.

An independent FDA assessment of novel excipients is needed outside of the drug application. The sponsor would indicate intended types of use and levels. We are not seeking approval of the excipient but rather a way to have the safety of the excipient evaluated and qualified for potential use in a particular route of administration and exposure level. This type of a

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system would give drug developers greater confidence to include novel excipients in drug products and facilitate innovation.

IPEC-Americas strongly believes that a novel excipient review program should not be limited to a new chemical entity but rather should include all different types of novel excipients. The vast majority of, quote, "novel excipients" are those that actually fit other types such as chemically modified grades of existing excipients, co-processed excipients, and current IID-listed excipients at higher levels of use or route of delivery.

So expanding the program to include these would go further to meet industry needs than limiting it only to new chemical entities, and the safety rationale for these is probably simpler than for the new chemical entities.

IPEC believes that all types of novel excipients should be candidates for the novel excipient review program and should be allowed for use in generic drugs, as well as innovator drugs,

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when their safety has been appropriately justified either with toxicology studies or bridging justification. A GDUFA/PDUFA type user-fee system could provide resources to FDA to perform these independent safety assessments or qualifications if needed.

In closing, excipients comprise greater than 90 percent of most generic drug formulations, and many are critical ingredients in drug product formulations contributing to how these products perform as intended when used by patients. Excipient issues need to be incorporated into the GDUFA III agreement in a way that will benefit FDA, industry, and the patient.

We request the opportunity to help ensure that the data in the IID are complete, consistent, accurate, and maintained as such throughout the data lifecycle. We also request the opportunity to provide expertise and suggestions on how a novel excipient review process might be developed and implemented.

Finally, we'd like to share our thoughts and

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concerns on guidance and policy for developing appropriate use of bridging studies. As FDA begins to define and develop GDUFA III commitments, IPEC-Americas' request an improved communication channel with FDA related to excipient issues and would like to be formally included in the GDUFA III discussions going forward. Thank you.

Clarifying Questions from the Panel

MS. NGUYEN: Thank you, Priscilla.

Now I will invite the FDA panel if they have questions for Scott, Diana, or Priscilla first. First we have a question from Rob Lionberger.

DR. LIONBERGER: Hi. This is Rob Lionberger. I have a question for Scott. You talked about the mid-cycle meeting not meeting expectations. Can you say a little bit more about what you would like to see at a mid-cycle meeting and at what point during the review cycles do you think this meeting would be the most valuable to industry?

MR. TOMSKY: Sure. Thanks, Rob, for the question. Look, I think I outlined it in my

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comments, but I think as was envisioned during GDUFA II negotiations, the mid-cycle review meeting, the whole purpose, from my perspective and I think industry's perspective, was an opportunity to see the initial review comments from the review staff and have an opportunity to discuss those questions to make sure that the industry was clear on the question being asked, as well as to ensure that industry is clear on what is required to respond to those questions to ensure that there's no follow-up question.

So really the whole purpose is to reduce the likelihood and need for a subsequent review cycle, and hopefully to try to work to achieve first-cycle approval. I think the current timelines are reasonable. Obviously, if we get them earlier, great, but I think the current timelines would be reasonable.

MS. NGUYEN: Thanks, Scott.

Jacqueline, I think you have a question next.

DR. CORRIGAN-CURAY: Yes. Hello. Thank

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you, Scott, and all our speakers for really laying out some very important points for us to think about.

Scott, I'm going to follow up. A number of our speakers -- you gave us a lot of things to think about in terms of regulatory predictability, complex generics, efficiency, and transparency, and a number of our speakers have talked about infections, and foreign inspections, and assuring the quality of the drugs as they're being made beyond review. So I wanted to get your thoughts about that aspect of GDUFA and where you see the importance of us working together on that.

MR. TOMSKY: Yes, sure. Obviously, my comments were limited to 15 minutes. I probably could have touched on several other areas. Obviously, facilities and inspection-related issues has been a topic of negotiations in the past and will certainly be an area of focus for GDUFA III as well.

I think one thing that jumps to mind is certainly the concern about the majors [ph]

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guidance, or the amendments guidance, or the [indiscernible]stands today, and the fact that any facility-related question resulting from an inspection triggers a major CRL. I think that's a huge concern. I think, as I have outlined in my remarks, it results in the overabundance or over-issuance of major CRLs.

So that's all I would say at this point, but certainly I think we will include additional comments with regard to your question about inspections and facility-related issues for generic NDAs.

DR. CORRIGAN-CURAY: Thank you so much.

MS. NGUYEN: Rob, I think you had another question.

DR. LIONBERGER: I have a question for Diana about the statement that PDUFA supports postmarket surveillance but GDUFA doesn't. Can you articulate very specifically what you think surveillance for new drug products should be looking for and what the surveillance of generic products should be looking for? Are they the same thing or are they

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different, from your perspective?
DR. ZUCKERMAN: Sure. Thanks for asking. I want to clarify that what I said was that the PDUFA does include user fees for postmarket surveillance, but MDUFA, the Medical Device User Fee Act, doesn't. I don't know whether GDUFA does or not. I looked online. I couldn't really figure it out, so it wasn't clear to me.
But to answer the second part of your question, yes, of course, there are differences, and some of those differences are based on the law and some are based on the reality. But I think that, obviously, the Sentinel program is a good example of something that is good postmarket surveillance for brand name drugs and also for generic drugs.
To some extent, the number of patients that you'd have access to studying would be much greater with generic drugs, but then if there are several different generic manufacturers making generic versions of the same drug, you might not know which one was taken.

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But I do think that some of the basic issues are the same, and that is adverse event reports, Sentinel, and real-world data of various sorts, and that would be big data but also other kinds of studies. I don't think that postmarket clinical trials would be likely for most generic drugs where they are done quite frequently with brand name drugs, but I do think that there would probably be times when that is the best way to find out what's going on if something serious seems to be occurring with patients taking a particular generic drug.
Then I talked about other things where FDA staff could be more available. I didn't mention in my remarks, but of course there's been a lot of talk today about meetings between industry and FDA, and those meetings are very, very important. But meetings with patients and consumers and providerswould also be very important.
Those meetings shouldn't only be focused on the backlog or how fast are these different generics going to get on the market; they should also be focused on whatever the patients think are

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important or whatever their concerns are, to be reassured and have more confidence in the safety and effectiveness of generic drugs.
MS. NGUYEN: Next is a question from Ted Sherwood.
MR. SHERWOOD: Great. Thank you. This one's for Scott.
Scott, you referenced the declining RTR rates as a success. Are there other successful areas that should be retained as we look towards GDUFA III?
MR. TOMSKY: Sure. Thanks, Ted, for the question. Again, I think the pre-ANDA, pre-development program has been a huge success, and we should continue to try to leverage it and build on that. Another area that I think has been outstanding has been the work done on the post-approval supplement side, and we've seen excellent results with the FDA review and processing of prior approval supplements, as well as CBEs [ph]. So those are a few things that stand out.

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MS. NGUYEN: Thanks, Scott.
MR. SHERWOOD: Thank you.
MS. NGUYEN: Does the FDA panel have any other questions?
(No response.)
Open Comment Period
MS. NGUYEN: Okay. I think there are no other questions from the FDA panelists for these three stakeholder presenters.
Next up on the public meeting agenda is the open public comment period. We have a number of individuals who have registered to provide brief remarks today. I will invite each person in turn to provide their remarks, and each person will have two minutes to present. When all of the open public commenters have presented, we will then provide an opportunity for the FDA panel to ask questions. When I call your name, please announce your name and your affiliation, please.
The first person to present during this period is Kristina Gehrki from USA Patient Network. You have two minutes.

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MS. GEHRKI: Hi. I'm Kristina Kaiser Gehrki. Can you hear me?
MS. NGUYEN: I can. Thank you.
MS. GEHRKI: I'm Kristina Kaiser Gehrki. I'm speaking today as an expert by experience and a board member of the USA Patient Network. Ten years ago this month, Stewart Dolin died of prescription drug-induced death after taking generic Paxil as directed for 6 days. Stewart was suffering from akathisia. Akathisia is a prescription drug-induced disorder caused by many different pharmaceutical products. These include asthma drugs, acne drugs, smoking cessation drugs, and malaria drugs, recently touted as possible of COVID treatment.
One large class of drugs that are known to cause akathisia and drug-induced suicide are SSRIs. SSRIs are products pharmaceutical companies commonly market as, quote, "antidepressants," end quote. I became involved with USA Patient Network and also the Medication-Induced Suicide Prevention and Education Foundation, called MISSD, seven years

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ago after my teenager, Natalie, died a similar akathisia-induced death.
Natalie's iatrogenic death occurred 2 days after she took the maximum legal dose of Zoloft as was instructed by her doctor. Natalie was not depressed, and the doctor who prescribed the ultimately fatal Zoloft dose did so by telephone without ever seeing my teenager Natalie. This doctor stated Natalie was not depressed, and again Zoloft had not been prescribed for depression.
It is a fact that most labels on generic drugs are incorrect. The FDA has also previously acknowledged that several generic drugs promoted as an antidepressant had never been tested, and in fact one was pulled from market.
Lastly, considering generic drugs may have different binders and fillers and do brand name products, consumers can experience allergic reactions. Many consumers of generic drugs also suffer adverse effects due to large increases or decreases in the amount of the active ingredient actually released in their bodies.

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Today I end my two minutes by urging the FDA to improve the safety of generics and increase warnings to patients and their doctors so that fewer people will suffer prescribed harm and death. Money from user fees is needed to improve patient safety. The speed of getting products reviewed should be secondary to the FDA's paramount responsibility, which is to ensure all Americans that pharmaceutical products they consume are safe and effective. Thank you for your time.
MS. NGUYEN: Thank you, Kristina.
The next commenter is Jonathan Furman also from USA Patient Network.
MR. FURMAN: Good afternoon, everybody. I'm Jonathan Furman, and I represent USA Patient Network. We are a group of patient advocates who are all familiar with the dangers of undertested drugs and devices that turn out to be dangerous.
My particular story involves suffering permanent harm from generic fluoroquinolone antibiotics. There isn't a day that goes by where I don't struggle with the aftermath of these drugs,

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which I took many years ago. Many of these side effects are currently on the label, but at the time they were not. Given that the drugs were generic and the warning label was clearly insufficient at the time, I'm particularly interested in how GDUFA influences the entire life cycle of a generic drug.
As you consider the implementation details of GDUFA, please keep in mind that low cost of production and speed of approval shouldn't be the only considerations. Safety and efficacy still need to be primary. GDUFA needs to make sure adequate provisions are made for inspections, postmarket surveillance, and most importantly for an environment that promotes accurate warning labels and timely useful risk communications to patients and prescribers.
Please don't think the time on market or generic status means that we completely understand any particular drug. The new information that we just all learned about the quinoline antimalarial chloroquine from our nation's COVID response perfectly illustrates this. GDUFA needs to be able

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to support clinical trials and other research initiatives post-market. Thank you for your time and consideration.

MS. NGUYEN: Thank you, Jonathan.

The next speaker is Peiling Cheng from Pharmaceutical Sourcing Partner.

MS. CHENG: Hello. Thank you for the opportunity for providing comments. This is Peiling Cheng from PSP, a small generic development company. My comments are related to the ANDA and your program fee.

The current large, medium, and small 3-tier structure seems to be simple, but it is putting much higher financial responsibility on companies on the lower end of each tier, especially for those in the small and medium tiers. If you're only one ANDA, the fee is $166,000, which is at least 5 times higher than the lower end of the spectrum, which is 33,000 per ANDA or 20 times higher than the ones on the extreme spectrum, which is less than 10,000 per ANDA.

So if you own 2 or 6 ANDAs, then you pay

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83,000 or 110,000 per ANDA, again significantly higher than the medium or the lower end. So we suggest in GDUFA III, this approach, which I call small household pays more taxes per person than the large household, be re-evaluated and implement a more equal structure which aligns with the resource allocation for the annual ANDA program, which will encourage more competition from small businesses so in the end the patients can benefit. Thank you for your time.

MS. NGUYEN: Thank you, Peiling.

This concludes the open public comment period. The final part of our agenda will be closing remarks by Jacqueline Corrigan-Curay, director of the Office of Medical Policy.

Closing Remarks - Jacqueline Corrigan-Curay

DR. CORRIGAN-CURAY: Good afternoon, and thank you, Martha. And I want to thank everyone who participated today. While we would have liked to be able to see you all in person, I want to especially thank FDA and all the folks who worked on the technical aspects to bring us successfully

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together virtually.

It has been an extremely informative and exciting overview of the successes of GDUFA, and a special thanks to our federal partners, our healthcare representatives from the American Society of Health-System Pharmacists and Kaiser Permanente, and of course GDUFA's partnership with our industry. I think David Gaugh from the Association of Accessible Medicines; Scott Tomsky from Teva; and our last speaker, Peiling Cheng from a small generic development company.

We also greatly appreciated the perspectives provided by Diana Zuckerman from the National Center and Priscilla Zawislak from IPEC-Americas. And finally, a special thanks to those who shared their personal stories, Mr. Jeffrey Furman and Kristina Gehrki. We know that's very difficult to do, and we thank you for sharing and making sure that we keep the patients in our first and foremost thoughts.

I want to thank all of my colleagues at FDA who've worked so hard to bring this meeting

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together. It's a team effort, but a special thanks to Martha Nguyen and Dat Doan, who's been active in driving us forward.

As we review the day, we see much has been accomplished through GDUFA by bringing high quality and affordable medications to the American public and meeting the demands in the time of this unprecedented pandemic. We've heard about the importance of generic drugs across our society, ensuring the health needs of our veterans, American Indian, Alaska Native populations, and our elderly.

The generic industry is meeting the health needs of all our citizens, and the success of the program is dependent not only on the diligent and efficient work on current applications, but we've heard about the need to be forward-looking and anticipating the future.

A key example we heard about today is GDUFA's robust scientific program, which has brought the best minds together to bring the next generation of generics to the market, including complex generics that can provide confidence to

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patients and practitioners that they will continue to meet their needs and be substitutable.

We also know how important the quality of generics is, and we heard about OPQ's approach to promoting quality across the life cycle and the opportunities in advanced manufacturing to further assure sustained quality. We also heard about our commitment from our inspectors to work with our industry to increase efficiency through the use of technology in partnership with our other regulators.

We are currently in the third year of GDUFA II, and what we've heard today is how highly successful the program has been, but it's also relatively young and still growing and improving. We thank all of our participants for reinforcing the importance of regulatory predictability while maintaining high standards to ensure patient safety; focusing on continuing assurance of quality and safety and accurate information for consumers and making sure that we have the resources to adequately support all of these activities,

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including inspections both within and outside of the U.S., and finally, the importance of transparency both to the industry and consumers.

We know there are opportunities to work together to continue to build on what works well and make appropriate improvements to further meet the needs of patients. We look forward to working with our industry partners and our other stakeholders to shape the future of GDUFA, and I want to thank you all for your attention and participation today, and my colleague at FDA. And with that, we will close meeting. Thank you.

(Whereupon, at 2:29 p.m., the meeting was adjourned.)

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