Public Meeting for Reauthorization of the Generic Drug User Fee Amendments of 2012 (GDUFA II)

October 21, 2016

A Matter of Record
(301) 890-4188

Page 1

FOOD AND DRUG ADMINISTRATION

Public Meeting for Reauthorization of the

Generic Drug User Fee Amendments of 2012 (GDUFA II)

Friday, October 21, 2016
9:10 a.m. to 12:34 p.m.

FDA White Oak Campus
10903 New Hampshire Avenue
Building 31 Conference Center
The Great Room (Rm. 1503 B & C)
Silver Spring, Maryland

Page 2

Meeting Roster

Robert Berlin
Office of Policy

Ashley Boam
Office of Policy for Pharmaceutical Quality

Mary Beth Clarke
Office of Executive Programs

John DiLoreto
Bulk Pharmaceuticals Task Force

Keith Flanagan
Office of Generic Drug Policy

David Gaugh
Generic Pharmaceutical Association (GPhA)

Robert Lionberger
Office of Research and Standards

Page 3

Ann Marie Montemurro
Office of Regulatory Affairs

Donal Parks
Office of Management

Gil Roth
Pharma & Biopharma Outsourcing Association

Ted Sherwood
Office of Regulatory Operations

Kathleen Uhl
Office of Generic Drugs

Page 4

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:10 a.m.)

Welcome - Mary Beth Clarke

MS. CLARKE: Good morning to everyone who's joining us. My name is Mary Beth Clarke. I'm the director of the Office of Executive Programs at the Center for Drug Evaluation and Research here at FDA. I want to welcome everyone, whether you're here in person or watching remotely, to the public meeting on our proposed agreement for the reauthorization of the Generic Drug User Fee Amendments. For the rest of this meeting, everyone will just be saying GDUFA II.

This is an opportunity, for those of you here and the public, to make your views known about the agreement. We have a very full day planned for you with some of our FDA officials who were involved in the negotiations or who will be leading the new program, assuming that it is passed by Congress, and they'll be talking to you about a number of the new things in the agreement: the performance goals; the program enhancements, which

go across the entire program both for application review and facility assessment; transparency and communication enhancements, which are extremely important and will provide greater accountability for the program for both our managers running the program and for our stakeholders, and for industry. And we'll also be talking about changes from GDUFA I to GDUFA II in the fee structure.

I'd like to take a second and reflect back to a little over a year ago when we had our first open public meeting on June 15th of last year, and during that meeting, we opened up the process for this reauthorization.

We spent some time talking about our experiences to date with implementing GDUFA I. We heard from industry. We heard from consumer representatives. We heard from individual members of the industry. And we also heard from healthcare payers. And several themes emerged from that, that were important for the agency to hear and that helped guide our negotiations, and I think we have responded to successfully in the new agreement.

First and most importantly, generics are vitally important to today's healthcare system and to the health of the American public. They were important in June of last year as we opened this process, and I think everyone here knows that over the last year, they have not diminished at all in the attention of stakeholders and the public, and their importance.

Second, the agency and the program heard the message, and that has continued to work faster, approve more generics more quickly, and give us a more robust generic drug marketplace for the United States, however, do not sacrifice quality. The public and our healthcare providers depend upon the quality of these products and being able to use them interchangeably.

Last, we heard a great deal, which we believe we responded to, in terms of making adjustments to the program both in its performance and in how the program is structured financially and how fees are paid.

So we hope that you will find as you hear

Page 9

the details today by the agency officials -- who are also joined by some representatives from the generic pharmaceutical industry trade associations. We have David Gaugh from the Generic Pharmaceutical Association; John DiLoreto from the Bulk Pharmaceuticals Task Force; and Gil Roth from the Pharma and BioPharma Outsourcing Association.

I'm not sure if our colleague from the European group is actually here to join us today, but we were fortunate to have a really good robust negotiating team, and I think we ended up with a good agreement. They will be joining our FDA officials up here for different panels.

I'd also like to point out to you, if you are interested in the full text of the commitment letter that is available online on our website. So you may study that, but we believe today will give you some very important context and some detail for how we arrived at the agreement.

After the presentations, there will be an open public comment period in the afternoon. We welcome all of your comments. If you did not have

Page 10

the opportunity to register in advance to speak, we will accommodate as many speakers as time allows. Written comments may also be submitted to the docket, which was originally available only up until I believe the beginning of November, and that has been extended.

There is a new Federal Register notice that is on display today and will be published formally on Monday that extends the docket until November 16th. And after all comments are received, the agency will consider those and finalize the proposed agreement, which will be then transmitted to Congress by the due date, which is January 15th of 2017.

If you have any media inquiries or any other questions, we ask you to take those to Kris Baumgartner and Sandy Walsh, our FDA communications staff who are here. I believe the trade press representatives are here, and you're familiar with them, and will take any questions.

I'd like to turn now to our first speaker of the day, Dr. Cook Uhl, who is the director of the

Page 11

Office of Generic Drugs here at FDA, who's going to give you some opening comments.

Opening Remarks - Kathleen Uhl

DR. UHL: Good morning. Let me echo Mary Beth's welcome, and thank you, Mary Beth, for those very nice opening comments.

First of all, I want to thank everyone who is here, whether you're here in person or on the WebEx, but thank you for your participation here today. I also want to sincerely thank everyone involved in the development of the GDUFA II recommendations. These recommendations reflect nearly a full year of negotiations with a lot of late nights, and long weekends, and extreme hard work for FDA and the industry staff that have been involved in these negotiations. I thank also the patient and consumer groups who have stayed engaged throughout the long process.

I have just a few opening comments. First, in terms of the big picture context, the Generic Drug Program has been, and continues to be, an extraordinary public health success story,

Page 12

absolutely. According to the IMS Institute of Healthcare Informatics, generic drugs saved the U.S. healthcare system $1.6 trillion between 2005 and 2014. So let me say that again, 1.6 trillion, with a T, a big T, trillion dollars over a 10-year period.

Nearly 90 percent of the prescriptions dispensed in the United States in 2014 were filled with generics, and I understand the most recent IMS report, that's now on GPhA's website, is 89 percent of prescriptions dispensed in this country are generic.

So these numbers speak for themselves. And if you can't put two and two together to understand how they speak for themselves, I will just say these numbers demonstrate the huge success of Hatch-Waxman and GDUFA I.

Second, I am extremely proud of FDA's Generic Drug Program staff. OGD, the Office of Generic Drugs, is really the center of the wheel. We are the principal public face of the program. But my office is just one part of that picture.

Page 13

The program includes many other offices across CDER and across the agency, including the Office of Pharmaceutical Quality, OPQ in CDER; many other parts of CDER; the Office of Regulatory Affairs; the chief counsel's office; and many other parts of the agency.

I salute the whole team, FDA's team and industry's team, for getting the job done. About a year and a half ago, I started telling everyone, as I've been reporting on progress of GDUFA I, that we built a machine, and now we're cranking it up, and our approvals are going to increase.

Most of the listeners noted my conviction, however, they were many times skeptical. And as a matter of fact, I think most people thought I was crazy. Well, we just finished fiscal year '16, FY16. We had approximately 835 tentative approvals and full approvals in FY16. This substantially exceeds our prior record of 619 combined approvals in fiscal year 2012.

So this 835 approvals and tentative approvals is the highest number of approvals and

Page 14

tentative approvals ever in the history of the Generic Drug Program at the FDA. And in the last four years alone -- so basically, the last four years have all been under GDUFA I -- we have approved over 2,000 ANDAs, and that's nearly 20 percent of all currently approved ANDAs.

On the other hand, the program has some persistent challenges. In particular, there are multiple review cycles for original applications. Historically, it takes on average 3.8 review cycles for an ANDA to be approved. So there's definitely more to be done.

Over the past four fiscal years, the agency has issued more than 5,400 complete response letters. This is a lot of first and second review cycles that have already been completed. We issue these complete response letters to industry to provide information to them about what deficiencies exist in those applications, and that industry can correct those deficiencies and hopefully lead to an approval.

So as we move deeper and deeper into these

Page 15

third and additional review cycles for this large bolus of ANDAs that are still not approved, the wave will crest, and our approvals will grow.

At the same time, it would be much better if we didn't have to review each ANDA multiple times to get it approved. The process is inefficient, and it's frustrating for FDA and for industry alike. It's not good for public health. Reducing the number of review cycles would be a highly impactful game changer. Thus, improving submission completeness and reducing the number of review cycles is the main objective of the GDUFA II program and the GDUFA II program enhancements.

FDA and the regulated industry are strongly aligned on this shared objective. Ted Sherwood and Rob Lionberger, who are up here, will walk you through the main program enhancements later this morning. The purpose of this meeting is to give the public an opportunity to present its views on the proposed recommendations, so we look forward to your comments today. In addition, the docket will be open until November 16th.

Page 16

So again, let me say one more time, thank you for your attendance today. We appreciate your engagement, and we welcome your input. Thank you.

Presentation - Keith Flanagan

MR. FLANAGAN: Good morning. I'm just going to provide a little background concerning GDUFA II and the reauthorization process. We're going to walk through why do we have a GDUFA I in the first place; what is an UFA; the result of GDUFA I; the statutory process for reauthorizing the program; why the proposed GDUFA II is very important; the main features of the proposed GDUFA II; and four major lessons learned and corresponding GDUFA II recommendations.

So first, why is there a GDUFA I? As Dr. Uhl noted moments ago, the Hatch-Waxman program has been an amazing success, approximately $1.68 trillion saved over the past 10 years and approximately 9 in 10 prescriptions are filled with generics, so huge successful law.

At the same time, the Generic Drug Program was chronically underresourced and could not keep

Page 17

pace with the growth of submissions. This became commercially unsustainable, and GDUFA I was enacted as Title III of FDASIA. This was the first ever human generic drug user fee agreement, approximately $1.5 billion in user fees over five years, and FDA's commitments were phased in over five years.

This is may be remedial for many people in the room, but just concerning the very, very basics, user fee agreements are negotiated by FDA and industry, then authorized in law by Congress and the President. And pursuant to the user fee agreement, industry pays agreed-upon fees, and in exchange, FDA fulfills the negotiated commitments.

At the first public meeting, about a year and a half ago, a year and a quarter ago -- we went into the details here. But basically, what GDUFA I enabled FDA to do was to execute a deep foundational restructuring of FDA's Generic Drug Program. I'm not going to repeat the entire presentation from last June. You can see it at our website, and the documentation is there.

Page 18

GDUFA I contained metric goals to improve the speed and predictability of review. We are currently achieving record levels of output, which we expect to continue to increase. As Cook mentioned, we had about 835 TAs and approvals in fiscal year '16, which dramatically exceeds our earlier record, and we think output will continue to increase.

We're confident output will continue to increase, improving access to quality, affordable generic medicines. Not to hop up and down about it, but it's worth noting that FDA has met or exceeded all of its negotiated GDUFA I commitments.

So there is a procedure prescribed in FDASIA for reauthorizing the program. Pursuant to sections 744C(d) of the Federal Food, Drug, and Cosmetic Act, the first thing we have to do is have consultation with shareholders [sic – stakeholders]. We've checked that. We did that. Second is the statute requires prior public input. So as noted, we conducted a public meeting last June 2015. Third, we're required to post minutes

Page 19

of the negotiating meetings on the website, which we did. And fourth, we conducted periodic consultations with patient and consumer advocacy groups throughout the negotiations.

So item 5 is public review of the recommendations. That's today's meeting. We walk you through the commitment letter, which has been noticed. The FR notice was also very detailed and explanatory, and we are soliciting your feedback. FDA's sorry to repeat this because it's a little tiresome maybe for you, but we want to stress the docket remains open through November 16th, and we welcome your comments. And finally, the recommendations are transmitted to Congress by the statutory deadline.

Why is GDUFA II very important? Because if we don't timely reauthorize, there are bad consequences, and if we do timely reauthorize, there will be good consequences. So the bad consequence if we don't have timely reauthorization is the user program pursuant to statute expires. This would create severe disruption in the Generic

Page 20

Drug Program. There would be staff layoffs affecting reviewers and our field investigators, and it would dramatically reduce program performance.

On the other hand, if the program is timely reauthorized, we would have a more efficient and effective review program; as Dr. Uhl mentioned, and Mary Beth as well I think, reduced cycles to approval, increased rate of approval, and we would be able to maintain and grow consumer access to generics.

The main features of GDUFA II, many of which other panelists will walk through in the rest of the day -- this is kind of a high-level overview -- ANDA review goals; ANDA review program enhancements; DMF review program enhancements; an enhanced pre-ANDA process for complex products; facility assessment enhancements; enhanced accountability and reporting; a program size commensurate with our workload; modifications to the user fee structure; and some small business considerations.

Page 21

So I'm going to walk you through four big lessons learned in GDUFA II and how the proposed GDUFA II agreement addresses that. Here's important lesson learned number 1.

In GDUFA I, our ANDA review goals were extremely complex and arcane. There was widely differential treatment of different cohorts and tiers of submissions, and in addition, adding another layer of complexity, because, pursuant to GDUFA I, ANDAs submitted prior to fiscal year '15, year 3 of the program, fiscal year '15, did not receive goal dates.

Industry sought additional clarity concerning when we might act on those submissions and some predictability so that they could do launch planning and conduct other types of important business planning. So even though the GDUFA I commitment letter didn't require or contemplate it, we assigned informal target action dates to thousands of submissions.

The long story short is that got us here. It created some kind of taxonomy over the entire

Page 22

large workload and charted a feasible path to our current state, where we're achieving record levels of output. On the other hand, it was very difficult to operationalize. And in addition, one result was a significant gap -- one result of the GDUFA I goals as negotiated was there was a significant gap between the formal negotiated review goal commitments on the one hand, and stakeholder expectations on the other.

For GDUFA II, we proposed that all ANDAs and ANDA amendments would fall within a single consolidated review goals scheme. This would simplify and streamline program administration and dramatically improve review efficiency. It would enable us to focus more on reviewing ANDAs and less on administering a very complex scheme. It would also reduce that gap between our formal goals on the one hand and stakeholder expectations on the other.

So my colleague, Ted Sherwood, will present some of these more detailed recommendations on panel 1.

Page 23

The next big lesson learned concerned the ANDA review process itself. The GDUFA I commitment letter described the ANDA review process at a high level of generality. The GDUFA I ANDA review procedures, when first operationalized by FDA, did not meet industry's expectations and were reportedly commercially disruptive.

There might be some -- I'm kind of understating the magnitude of that, and there are some smirks from industry in the audience. So we had a lot of work to do, and FDA made some adjustments. Applicants saw much more communication and much more transparency.

For GDUFA II, the proposed ANDA review procedures are much more specific and programmatic than corresponding features of GDUFA I. They refine and enhance each stage of the ANDA review process from start to finish.

There is much more communication and transparency in general and at key points in the process. Roles and responsibilities, sequencing and timing, are prescribed in detail, and there are

Page 24

more opportunities for applicants to address deficiencies within the current review cycle. That's a big deal. That is intended to reduce the number of cycles to approval. And again, Mr. Sherwood will produce the details on panel 1.

The third big lesson learned from GDUFA I is complex products pose distinct scientific and regulatory challenges. Applicants sometimes don't know what FDA expects at the front end, so it is harder for them to develop approvable ANDAs for submission. Then what happens is because of that, after submission, there are often a lot of review cycles for complex product ANDAs, and a huge amount of back and forth between FDA and applicants. This is highly inefficient.

So for GDUFA II, we propose an enhanced pre-ANDA process for complex products. The big-picture concept is we want to frontload work so that the ANDA can be right the first time when it's submitted.

FDA will issue a guidance concerning this. We want to target this program so it will be sure

Page 25

to improve review efficiency. We want to mitigate operational risk. And what that means is we still have a lot of ANDAs in house, and our review staff needs to spend a lot of time reviewing those ANDAs so we can get products out. If we're swamped by a high volume of low-impact meetings, that takes time away from review activities.

The third thing the guidance will need to do is manage stakeholder expectations. FDA and industry both definitely and strongly want to do this, but I want to clarify that this is targeted. It is not a broad, open-end invitation to consult with FDA, although there are some features in there like control correspondence and other such features, so there are other consult opportunities, and the applicant still has the primary responsibility for developing the ANDA. And Dr. Lionberger will present some of the more detailed recommendations on panel 1.

Complex products are a relatively small part of our overall workload but can consume a disproportionate share of resources, so we think it

Page 26

is going to impact review efficiency a lot.

Fourth lesson learned from GDUFA I, in GDUFA I, FDA and industry projected that FDA would receive approximately 750 ANDAs a year, and the agency planned and budgeted accordingly. We actually received approximately a thousand ANDAs a year, and if you look at fiscal years '12 through '15, we got the equivalent of an extra year and a half of work.

In addition, as I mentioned before with respect to the target action dates, thousands of pre-year 3 submissions had either no or very modest GDUFA I goals and resources, but FDA still needed to review them, and it usually involved multiple cycles. So there was a pretty significant gap between FDA's resources on the one hand, and our workload, stakeholder expectations, and public health needs on the other.

So for GDUFA II, we proposed that the program should have resources commensurate with our overall workload. And Mary Beth Clarke will present the details on panel 2. And that is it for

Page 27

me. Thank you.

Presentation - Robert Berlin

MR. BERLIN: Great. Thank you very much. My name is Rob Berlin. I'm a senior policy advisor in the Office of Policy within the Office of the Commissioner. I'm going to walk through a broad overview of the landscape of the generic drug industry, and in particular looking at small business and possible small business relief from fees.

The small business group was formed to provide a forum to discuss the characteristics of small businesses and included representatives from each of the trade groups, along with CDER and the Office of Commissioner for FDA. We were formed to address both congressional concerns reflected in congressional reports asking that within GDUFA II, we consider relief for small generic drug manufacturers.

In addition, the group was formed to reflect concerns that both FDA and industry had with regard to the fairness and appropriateness of the fee

Page 28

structure as regards to small business.

The group considered approaches, first off, to get a sense of the shape and size of the industry to defining small business, looking at the potential, to look at the number of ANDAs approved either for an applicant or at a facility. We looked at revenue, and we looked at employee numbers.

This work was greatly helped by work from our economists who had looked both at submission information to FDA in terms of facility payments and application numbers, and also match that through internet searches, Dun & Bradstreet research, to try to understand affiliate relationships between different entities.

In considering approaches to fee relief, industry suggested several ways we might look at this. For instance, we looked at small business relief in the form of a discount or waiver on the fee for the first application that a small business would submit as an ANDA. In addition, we looked at an issue that we've sort of termed payment while

Page 29

pending, so the idea that entities would be paying a facility fee before there were any approved ANDAs produced at that facility.

So working through a variety of these possible options and different ways to approach it, we discussed the practical impact of the proposals, an obvious being any relief provided to small businesses is going to distribute cost to others. Likewise, if you have a process for people to request waivers or to seek relief in some form from fees, you have a burden on the applicants to produce information to support that, and likewise, you have a burden on FDA to administer that program and review information that would come in.

At the same time we were talking about these issues, there were two very significant fee issues that fell outside of the small business group's work, and the group intentionally put these issues to the side while acknowledging the discussions in the group would affect our review of these issues and vice versa. And those issues were the overall program cost and the split of the fees between

Page 30

applications and facilities; and within facilities, between different players, applicants who also have ANDAs, contract manufacturing organizations that were making finished dosage forms, and API manufacturers.

So starting with looking at the characteristics of the ANDA sponsors, what we found is most ANDAs are from large firms. Approximately two-thirds of ANDAs come from companies whose parents have revenue of over $100 million. Likewise, for the sponsor facility, so applicants who have facilities themselves, most applications come from entities who have over a hundred approved ANDAs already.

By contrast, when you look at sponsor-only firms that are smaller and more likely to be domestic, often they would have under $10 million of revenue. So these are entities that don't have any facilities. They have under $10 million of revenue, and often less than 10 approved ANDAs in their portfolio. And notably, there is a shift over time towards consolidation and movement

Page 31

outside of the U.S., but what you get as a picture is kind of two poles.

You have a lot of applicants where you have many applicants forming your lower end of it, your lower revenue, lower approved ANDA numbers, and then you have a lot of very big parties with a decent size middle, but you have these significant poles.

Additionally, we looked at the characteristics of facilities. You see most API and FDF facilities are part of large parent companies, most having over $100 million in revenue with a small portion under 10 million. But when you break it down, what you see is most API facilities are larger, sponsor facilities are larger, but facility-only operations are small to mid-size, with most having revenue under $100 million and many having revenue under $10 million.

So as we worked to think about how we would implement any program and how we would consider any relief that might be appropriate, the first

Page 32

challenge we really wrestled with is how do you define small business, and the number of employees, the revenue, and number of ANDAs. And even within some of these categories, you look at revenue, for instance, we found is it appropriate to be looking at revenue that a company has or is it appropriate to be looking at the resources that a company has, so what support they might have for any work.

Some of them you'll find -- some companies would be small under all of these definitions. For instance, a start-up could be small under all three criteria, but at the same time, they may have a lot of support behind them in terms of venture capital that could be introduced and perhaps a plan to get applications approved and move on in a different way from there, you're selling applications, et cetera.

By contrast, you also have entities who are small under some criteria but not under others. You might imagine a large company that's new to the generic space will have many employees, significant revenue, but at the same time will have a very

Page 33

limited number of ANDAs. Likewise, you have some contract facilities that have limited employee numbers, limited revenue, but have quite a significant number of ANDAs at their site, but they're not actually producing as much because they may be listed in applications but not being the primary facility used.

So overall, you get a picture, as I suggested, of a substantial number of large firms, but at the same time, a very significant component that's small, which makes it very hard to think about exactly where one would draw the line between small business and larger entities.

This becomes particularly challenging as we looked at the API and finished dosage form manufacturers who are non-sponsors. And there you see there's a significant amount of uncertainty about the size of the industry, so you have a lot of entities that are private. You have a lot of entities that are overseas. And with those, it becomes very hard to both know the size of the entity and to know what its affiliation status is.

Page 34

So as we were working through the data, you end up with a significant portion that you can't fully predict, and it makes it hard to think of how you would appropriately set numbers.

Likewise, if you're thinking about how you're going to administer that program, it's very challenging to think about what sort of information would you expect to see from industry in support of an application for relief, perhaps looking at their financials, et cetera.

It's a significant burden on FDA as well to look at that information and either provide -- if we have a very high amount of scrutiny on these applications, it's going to take a lot of resources. On the other hand, if you don't, you may have inequity between the different groups as to how they're treated.

After looking through a lot of this information, we really concluded that a lot of the traditional models of small business fee relief didn't make a lot of sense here. They would have very high administrative burdens and may not get

Page 35

relief to the behaviors you're trying to drive and trying to ensure that people are able to participate in the market.

So ultimately, the fee structure that will be discussed later this morning by Mary Beth reflects a lot of the work we've done and an understanding of industry that comes from that, and really as an effort to match the program fees and costs to the activities that FDA engages in to respond to industry demand and needs. And while we'll talk through these quite a bit more, if you look, issues like tiered program fees to get at the burdens from different applicants, the ability to pay, and how much applications are putting into the agency was one approach.

We looked at the fact that CMOs tended to be smaller businesses and often were in more need of relief. We looked at that in terms of the total fee that the CMOs would be paying as compared to ANDA holders. Likewise, one of the issues that we did raise that will be discussed further and is in the fee structure as now considered is to have no

Page 36

payment while pending. And that's the idea, again, that while an applicant is waiting for an approval, or for the company with which they're working to gain an approval, they won't be paying a facility fee during that time.

So with that, I'll turn to any questions people might have.

(No response.)

MR. BERLIN: I'll introduce next Rob Lionberger and Ted Sherwood from FDA, and David Gaugh from GPhA as well. Thank you very much.

Panel 1

MR. SHERWOOD: All right. Good morning, everyone. My name's Ted Sherwood. I'm with the Office of Generic Drugs on the operations side. This is one of these key moments in the life of an operations person, where you're both excited and scared as you go through and look at some of these things. I think a lot of people in FDA would probably have the same sentiments.

We'll break this off into two sections. The first one is looking at the performance goals.

Page 37

This is what gets people excited and certainly makes a lot of the public postings that we see about FDA. Since this is the transition, we're going from GDUFA I into GDUFA II, we're keeping those key metrics.

It's a mature program, so we're working at 90 percent. We're going to carry that into GDUFA II. For many of the metrics we're going to be talking about and certainly when we look at the application performance, that's a very standard metric that we see with healthy user-fee programs across the entire agency.

When we look at the specific goals, we're going to continue to work on the 10-month clock that's new to this year, and that will really push FDA to hit its maximum efficiency in terms of working on both the review parts of the application and the facility assessments. And the facility assessments is the key to the next part.

For priority applications -- and here we're carrying over the same definition now, public health, drug shortage, first generic, sole source,

Page 38

those kind of things. These are more important products. We want to get those out on the marketplace. We want to provide that to the public. We are now going to take one of these scary moments and allow the companies to submit the facility information in advance of the actual formal ANDA. This is to allow us to get a head start on making the assessments and even working the potential steps to get an inspection executed, if that's necessary.

Then the actual application will come in a couple months later, and we'll start the more traditional review. And then we'll have to merge those two separate entities into one FDA decision. So this is certainly an area where you see a lot more information from the agency as we move forward and pull all these pieces together.

But this is an exciting opportunity. We now have the ability to bring these important products out to the market sooner, so we're looking forward to getting these high-quality applications into this specific priority program.

Page 39

Then we have the amendments. For the applications that don't get approved under one cycle, which is a common occurrence and one that we'll certainly work with industry to try to mitigate as much as possible, we need to have something in place.

So here's the structure. And again, what you'll see is faster times for the priority applications and really highlighting the fact that all the way through the life of that priority application, it is going to go to the express line within the agency. So we're going to give it a thorough review, but it is not going to be waiting and held up at different spots. We will grab it and work on it as it comes in.

Then we have the minor amendments, and this is sort of a reflection of what's going on today, where we've worked to hit the sweet spot; what's the best we can do in terms of getting an application amendment into the program, getting it triaged uploaded into the platform, into the reviewer's hands, hopefully ready to go and make

Page 40

that approval decision, where there are all sorts of administrative efforts that get added on to that package as it moves in for the final stamp of approval.

Then we get into the supplements. Right? You have that approval. Companies are going to go out there and make changes and hopefully advance their product. We've broken this off very similar to what we've done in GDUFA I, ten months if we need the inspection; six months if we don't.

Now for the priority applications, we've added again that eight months fast track if the company can put forward a successful pre-facility communication. Let us know what the key sites are just as you did on the original applications. We'll start that process rolling in advance of that formal supplement coming in.

Then for amendments, same thing, carrying over many of the goals from GDUFA I, but again now putting extra effort and attention on the priority products and moving those through. So we're going to get those changes. If it's an essential

Page 41

product, we will do whatever it takes to get that change executed so the companies can go to market based on that change.

Then again, for the majors and minors, finish the major, get into the minor stage. We're going to fast-track all of those through the system. These are cases where very small changes are needed by the company to hit the standard. We're going to take that and work it through as quickly as possible.

Then there's a section on unsolicited amendments. Much of this is carried over. The key, as in GDUFA I, the latter of the dates of the type of change and the type of submission that's being submitted to the agency will determine the appropriate goal for that amendment.

Drug master files, we're going to continue the success of GDUFA I and really highlighting this as a separate very special review element in its early stages and then as it gets linked into the final ANDA decision. So in the early stages, the complete and initial assessment is going to be made

Page 42

for 90 percent of these, so certainly a lot of work to make sure all the pieces are in place for those applications when they are finally submitted to the agency.

Controlled correspondence, often times is part of the R&D process for the companies. We're going to work the standard ones through, 60 days, as we're doing now. For complex products, this is actually a slight extension, from 90 days to 120 days, to allow the agency more time to provide a more substantial meaningful response to the inquiries. So this is designed to help companies understand the target where there isn't specific guidance and regulation, things like that, already in place.

New to this program is allowing formally now the companies to call in and say, hey, we've received your answer. It was on time. Great. However, I still have a question. Section 2, I don't understand this little nuance. Can you explain it or here's what I was getting to with my question. We will entertain those. We will take

Page 43

those through. It's in both of our best interests to make sure there is a clear understanding of the target for this potential product.

Then bridging. As Keith Flanagan indicated, there's a lot of work already here or a lot with the companies that could come back into the agency before GDUFA II is kicked off. We are going to manage those. The dates that we put in place for those correspondences, the amendments, originals, things of that nature, those are going to be honored by us as we cross the bridge into GDUFA II.

Then any new submission sent to the agency, starting day 1 of GDUFA II, gets the GDUFA II date. It fits that scheme we talked about, whether it's a two-year-old application or a 20-year-old application that's still struggling through to the finish line, if you make a submission after October 1st of next year, you are going to get the GDUFA II full-court press.

Switching sections now, looking at some enhancements to the program -- and this is really more than just review; it's all the efforts and

Page 44

communications that go along with it -- it starts with the application received. We know that. That's a key first step: defining the bar, helping companies hit that bar, and then screening to make sure that the applications do have all the right pieces.

We're going to strive to make those decisions within 60 days so that we can turn that work over to the review programs. We're going to have now a formalized information request process built in there.

So if the company has minor issues, or we think the data may be in the application, it's just not presented in the way that we're connecting with, we're having trouble finding it, we see summaries, they must have had the data, it's a significant application, they got certain points, the other points must be buried in there somewhere, then we will work with the company to try to find those, make sure everything is in fact within that application, and allow that hopefully to move forward into the review teams.

Page 45

Then we're going to be notifying the applicant, at the time we make the decision to accept your application, whether or not, you are standard or priority review. You will know that. That will help then to define the goals, and it will be an indicator to you when you can start to expect to receive further review communications from the agency.

We're going to issue the IRs. In fact, many people are familiar with those. We're going to expand and take one of the successes off of the new drug program, the discipline review letter, and apply that now into the generic program. This is very important. This is again one of these exciting and scary features.

We are committing to providing a mid-point response to the applicant. We've done our work. We've gone through the application. We've collected information from all the disciplines. Here's a preliminary finding by the agency.

This is a big game changer. We're going to continue to issue IRs and these DRLs throughout the

Page 46

life of that cycle. So if we give the company a dot-the-I, cross-the-T type of change at the mid-point, and they quickly turn that around, we will keep reviewing. And if there's time, we'll even do another round; here's one more I that has to be dotted before we get to that final stamp of approval. We will work with the companies as much as the schedule -- and this is where it works with both the review and industry timelines, feeding together to make this successful.

Some of the other new features are we will work through the goal. We will miss the goal -- we own that -- if we can take an important product and bring that imminent approval. So if the company is on the edge, one quick little update and you're ready for approval, we will work with you. We will miss that goal to get the good products out on the market whenever they can.

So we're certainly watching and very conscientious of when we think the first commercial marketing date will be. We will drive our program to try to hit that. And of course, as we do now,

Page 47

we will continue to send the responses when we have them. If we're done early, we will provide the response early. When we're done, we will send it out.

We're going to pass on different signals from the regulatory project managers. So if we get information from one of the review disciplines that something substantial has gone wrong or is missing, we're going to communicate that right then and there. "Hey, regulatory affairs colleague, I'm not sure how all this is going to play out, but I was talking to the discipline; they have some big issues. They're going to be providing very specific information soon, but I wanted to let you know as soon as I did that this application has some additional hurdles before it's going to be ready." We want the companies to understand that and use that to help in their planning for this product or other products that they may be working on.

If we realize we may miss a goal -- maybe it's a good reason we're missing it, to try to turn

Page 48

it into an approval, are there some other complex issues associated with it -- we're going to inform the applicant, here's what's going on, here's the status to date, here's why we think we're going to miss that goal, here's when we think we're going to be able to communicate to you.

We will allow the companies to contact us, periodically. We don't want phone calls every day, but we will allow them at key decision points within the company to say, hey, one of these cruxes, we need to figure out whether they're going left or right with this product; what's the status? We will go in there discipline by discipline, this one's ready; this one's on the verge of being completed; this one hasn't been started yet. That's the kind of information we will do to help the companies navigate this process.

We're going to include, any time we make a decision, to change the priority status of an application. The issue's been resolved. Maybe it's no longer priority, or we've gotten word that there is a potential issue emerging, potentially a

Page 49

drug shortage or something like that that could change during the life of that application. We will work to make sure companies understand that.

When we issue major deficiencies, we will explain them. We will explain why we think they're major. We understand that's going to have significant impact and obviously lengthen the time of the response from the agency. So we'll explain, these are the five things that are wrong. Here is why we think this is going to be a major effort for us to review the additional data. We're going to have to go back nearly to step 1, so on and so forth.

We're going to allow companies to continue to send in requests for complete-response telephone conversations. "You've issued those five deficiencies to me. I'm not sure what number 4 means. I want to sit down and talk with you." We will allow a face-to-face discussion of those. So the companies can work through the process, and we will arrange to get the right people at that phone call to explain, here's what we're seeing, or in

Page 50

some cases what we're not seeing. Here's what's needed. Here's what we think would help close that gap. Again, make sure everybody understands the target that will help the applications flow through much faster. So the hope is, after this telephone conversation, the responding amendment comes in and can be moved very successfully towards approval.

We talked about changes. One of the key things that we will do when we change the status of an application, which is rare but certainly a big event for the companies, we will allow them the opportunity to come back and sort of question the decision. "Here's why we made that request, FDA. Here's what we think is going on and why it supports our request." And we at the agency, then, will respond. "Here's our information or here's the interpretation of the regulation. This is why we said you're in this lane versus the other lane."

So this is going to help companies have a better understanding of what it means to be standard versus priority review.

Then of course, as we said before, we are

Page 51

going to champion the applications. We want them to be approved. We need them to be approved. That's what helps us fulfill our mission, getting the drugs out to the public. So we will work to get the good applications approved hopefully at a higher rate within that first cycle.

Having those mid-point touch points is going to be very important to this; tell you the information in the middle of that review process, give you the expectations, and give you an opportunity to provide that, get those last pieces of those puzzles in place so we can make an approval at the end of that first cycle. That's the goal that we're working towards.

Obviously, for the important products that have those key dates -- and I think the companies are very aware of those -- we are going to do whatever it takes on our end to make sure that we can hit those dates. So companies that submit their applications in a timely manner, have the right pieces in place, they're going to get championed to hit that date. And that same logic

Page 52

applies to the tentative approvals. We understand that that's a very important metric for the companies, and it sets them up for success and hopefully soon to get on the marketplace.

We have a new program on dispute resolution. We have it now. It's informal. We're going to make it formal. We are going to take the existing successful program under PDUFA, on the new drug side, and bring that into the generic program. And one of the steps to that is an informal dispute request. We are now designating a position within the Office of Generic Drugs to help the companies navigate that. They will help explain the process, link the applicant in to the right area to get that potential dispute resolved.

We have goals on this; new program. We're going to slowly build this into place, but we are committed to working with the companies so at least they understand the environment, they understand the rules of engagement, and they know how to put together a successful dispute.

Then we're going to continue to advance the

Page 53

program. Even if it's not outlined in these goals, what some of our colleagues are going to be talking about, we are continuing to move the program forward. As we see ways to do better business, to communicate more efficiently, we are going to take advantage of that.

So it's a tremendous amount going on to have all of this come together, but we're excited. This really gives us the opportunity to get the products out there. And one of the keys to this, into making all this a success, is getting the right target out there, and Rob Lionberger is going to talk about that. Thank you.

DR. LIONBERGER: Good morning, everyone. I'm going to talk about our pre-ANDA program and specifically its impact on complex products. Before we do that, we have to define what we mean by complex products. There's a formal definition of complex products in the GDUFA II commitment letter. It talks about products with complex active ingredients, formulations, routes of deliveries or dosage forms, complex drug device

Page 54

combinations, or other products where there's unexpected complexity or uncertainty.

So this definition is really intended to exclude from complex products solid oral tablets and capsules, oral solutions, and simple solution injectable products. Those products are the vast majority of our workload. Those are what we consider standard products.

The complex products include things like complex mixtures, locally-acting drugs, novel dosage forms. The complex drug-device combinations are products like metered-dose inhalers, in addition to being a drug and device, but also have significant patient use issues that require additional discussion around those products.

So we think that we focus the attention for complex products on the ones that have scientific challenges that are harder to develop, that need more attention through the pre-application review process.

Under GDUFA II, there's a proposed pre-ANDA program that goes beyond complex products. So the

Page 55

things we'll talk about here are not just limited to complex products, but there's a special focus on making sure that they meet the needs for complex products. But now under the proposed GDUFA II, we have an integrated pre-ANDA program that includes meetings, product-specific guidances, regulatory science components, the control correspondence process, and inactive ingredient database improvements that should broadly accelerate and clarify requirements for application submission.

In GDUFA I, we were doing a lot of these things, but there weren't commitments around all of them. Now, in the GDUFA II commitment letter, there are commitments in all of these different categories, so we have an integrated program in the pre-ANDA space that I think will give companies clarity on where to go to get the answer for specific types of questions.

Now, one of the things that's completely new in the commitment letter are the meetings. The meetings are specifically focused for complex products. There are three types of meetings that

Page 56

are described in the GDUFA II commitment letter. If we go sequentially through the product development life cycle, the earliest type of meeting is what we call a product development meeting. These are meetings when you're developing a complex product, you're trying to identify what are the appropriate bioequivalent standards for this product, what are the challenges in development. These products are difficult because there are complex scientific issues.

So these meetings are focused on the scientific exchange, on specific issues with the expectation that there's work and preparation from the potential ANDA applicant before they come in, and then that allows FDA to provide appropriate feedback to advance that development program early in the process.

As you proceed through product development, there's an opportunity also for what we call pre-submission meetings. So these are when you have your application all put together, it's a complex product. So it may be things that FDA ANDA

Page 57

reviewers don't normally see in an application.
The pre-submission meeting is an opportunity, some time approximately a year before a submission, to really walk through the review team about what's going to be in the application, what's going to be new, what are the types of data that you're going to see. It's not a substantive pre-review, but it gives opportunity for FDA to point out, these are things you might need to clarify to make the review go faster.
The pre-submission meetings also are the opportunity where FDA's review staff will align the scientific staff that have been talking to you in the product development meetings with the people that will be reviewing your ANDA process. So it will be a transmission of information also internally to make these product submission meetings a linkage between the earlier discussions and the ANDA review process for the complex products.
Finally, even when you're in the review process for complex products, there's an additional

Page 58

aspect of a mid-cycle review meeting for the complex products that have had these pre-ANDA meetings where you'll get the opportunity for a teleconference with the review team after that initial set of discipline review letters, where the initial issues have been identified. And this is an additional opportunity to accelerate the development and review of complex products.
So to explain how this system will work, we will be issuing a guidance on the meetings, which will describe how these different meetings work; how they're integrated; what the expectations for the data packages are; where you send the packages; what types of requests you'll get back from FDA with respect to the meeting granted; how we'll schedule them; what we'll do in the lead up to the meeting; and how we'll provide the minutes and the conclusions from the meetings to you.
One aspect that's in the commitment letter is what we call an integrated meeting track. For a complex product development program, once you're granted that product development meeting early in

Page 59

the process, then you'll be eligible for the pre-submission meeting before your application comes in and for the mid-cycle review meeting. So there's a real integrated track that links those meetings together once you've entered into that type of interaction with FDA. And I think this will really link through the pre-application discussions into the review process in a very effective and efficient way.
In the commitment letter, there are goals for the meetings. You're going to be guaranteed a meeting decision in a timely manner. In all cases, there's a phase-in. In the first two years, we'll get you a meeting decision within 30 days, and then after that, within 14 days you'll get a decision whether the meeting is granted. And then the meetings will be conducted within 120 days from those decisions. There's no limit to the number of meetings; I'll talk a little bit about that on the next slide as we move into the product-specific guidances.
In the product-specific guidances, I think

Page 60

many of you are familiar that the product-specific guidances identify primarily bioequivalence methodologies but often times for complex products, additional information. There are approximately 1600 of these guidances on our web page now. They're a critical part of the current review process. They're one of the big reasons why the first cycle acceptable rates for our bioequivalence reviews are very high, because we're very clear about what the bioequivalence expectations are.
So now in the GDUFA II commitment letter, there are goals related to the product-specific guidances for non-complex new chemical entities, we have a commitment to have those guidances available two years before the earliest lawful filing date. So you can get the guidances before you start conducting the studies for those products.
For the complex products, there's no commitment on the guidances. We're going to provide guidances as soon as the scientific recommendations are available. But in the negotiations, there's an incentive process for us

Page 61

to get those complex guidances available. In the meeting process, if there isn't a guidance available, we will guarantee that we will meet with you if you have an acceptable meeting package. So for places where there's a complex product and we haven't yet put out a guidance, those will be prioritized for product development meetings.

It's in FDA's incentive to provide timely guidances, but if we're not able to do that, that is where you'll have the opportunities to discuss an individual development program with FDA through the meeting process.

The meeting process also prioritizes for complex products, cases where FDA puts out a guidance, but you think there's a scientifically sound alternative approach that may be more efficient that may lead to faster access to generic products. Those types of meetings are also prioritized under GDUFA II, and we will grant those meetings as well.

So even if we have a guidance, but you think there's an alternative approach, those two types of

Page 62

meetings are the ones that will be granted when there's an acceptable meeting package. Other meetings will be granted based on the workload availability and the value to the review process.

For other product-specific guidances, we'll continue our current practice. Through the generic drug mailbox, the industry can request guidances. This makes us aware of products where we may not know that there's an interest in generic drug development, and so we can factor that into our planning and make those guidances available to facilitate drug development.

We will also in our internal process prioritize public health priorities. If we know there's a drug shortage, we'll try to ensure that there's a product-specific guidance available so that the requirements for generic products are as clear as possible in that space.

There are multiple other aspects of the pre-ANDA process that are described in the GDUFA II commitment letter. Ted mentioned the goals for controlled correspondence add a separate category

Page 63

for complex controls. This also allows us to expand the scope of questions that we will answer through the control process. So the complex control process in the commitment letter talks about questions of the clinical impact, but it also talks about places where there might be a product-specific guidance, and you might be proposing an alternative approach.

For example, a product-specific guidance talks about having a parallel pharmacokinetic bioequivalence study, and you think for this drug a cross-over study would be appropriate, that would become a complex control correspondence that gives us enough time to do the detailed scientific analysis to give you an answer for those questions.

The complex control correspondence is also the place that you will go for bioequivalence protocols that are related to products that have REMS with elements for safe use that lead into the safety determination process, you'll have a commitment on the timeline for those protocol reviews.

Page 64

The commitment letter also has regulatory science enhancements. It has improved commitments about linking the outcomes of our regulatory science activities to guidance development. It has a new process for gaining industry input into regulatory science priorities through formation of industry working groups that will be able to meet with FDA multiple times during each year to make sure that industry input is clearly provided to FDA, and it allows us an opportunity to explain what we're doing in each priority area.

The inactive ingredient database enhancements are in the commitment letter. These will provide new information on what we think is a critical pain point for industry in terms of the maximum daily exposure for each excipient, not just the amount that's in approved products. This is a big gap in the current inactive ingredient database that's a pain point for industry, and we have a commitment to address that and provide much better information in that case.

The safety determination letter, once the

Page 65

protocol is reviewed through the complex correspondence process, there are specific timelines for getting a safety determination letter that may help access to products that are difficult to acquire in the marketplace.

Finally, if we look at the pre-ANDA program as a whole, the intention is that it's going to clarify expectations for prospective applicants early in product development. For complex products, you'll have specific access to meetings and a meeting track that should provide the necessary direct interaction on those more complex products.

All of these aspects of the program will help applicants develop more complete submissions: the inactive ingredient database, control process, timely availability of product-specific guidances, all are linked to better submissions. Better submissions and having this information decided up ahead should lead to an effective review process. We don't want a situation where a complex application comes in, and it's on the 10-month

Page 66

clock, and we have to decide what to do in those 10 months.

Through these pre-ANDA processes for those complex products, we have our scientific, our regulatory staff, all of the internal FDA stakeholders aligned before the application comes in, and then the application review process can focus on reviewing the data that comes in and not deciding what's acceptable just at the time the application comes in.

When you put all of these together, they should be reducing the number of review cycles, especially for the complex products, where we've seen some products go into double-digit review cycles because we're figuring out what we have to do while the application is under review. The goal of the pre-ANDA program is to figure out all of those requirements before the application is submitted.

Thank you very much, and I think this is the time for questions, not just for me, but also for Ted as well, and David.

Page 67

(No response.)

MS. CLARKE: Hearing no questions, we will take a break. We are running a little ahead of schedule, so we'll just make it a little bit longer. If folks could come back by 20 minutes of 11, I think that will give everybody an adequate period for a break, check email, whatever we need to do. We'll resume then.

(Whereupon, at 10:19 a.m., a recess was taken.)

Panel 2

MS. CLARKE: So we'll go ahead and get started now with our second panel on the proposed new fee structure. I'd like to acknowledge we have a few other people who have joined us now here, Donal Parks from CDER's Office of Management, and we're joined with three of our trade association representatives, John DiLoreto, David Gaugh, and Gil Roth.

I think it's particularly important for us to have them up here for this portion because at this point, we're really not just representing the

Page 68

agency's portion of the program, but really this is the heart of the negotiated agreement. And I think, as most people will readily understand, it's one thing to talk about what's in an agreement and what we want programmatically. It's a whole other conversation to talk about how much to pay for that and who gets to pay what, which is about the fee portion. So we're going to try to enlighten you on those things.

The commitment letter that we've referred to several times and posted on our website does not have the detail on the new fee structure. That's actually in a separate summary. That's just generally -- I would do that because the other details of that are in the statute, not in the commitment letter. So right now, the summary is what is available.

The first thing I'd like to talk about are a few -- I'm going to talk a little about the things that we had to grapple with in terms of establishing the overall program size, and then we're going to get into more fee specifics as we

Page 69

move through this. And we're going to end up at the end of this session also talking about some pieces of the agency's financial management of the program and how we go about doing our work analyzing the need for our resources and how we assign those.

So first of all, it's been mentioned a few times, GDUFA I assumed that FDA would receive approximately 750 ANDAs per year. Those of you all who are insiders or have been with the program for a while may find that surprising because before GDUFA I launched, the number actually was at a thousand. But there was a thought on the part of both the agency and I think industry that the introduction of the new fees might actually result in a decrease in the number of generic drug applications; certainly not something the agency or the industry hoped for, and in fact turned out not to be the case. If anything, the number of applications coming into the program continued to increase.

But that was the number that was used for

Page 70

the baseline budget projections, and so it's an important thing to note that that number continued to go up. It is our baseline workload. So an important feature of GDUFA II is that we've sort of resized the program commensurate with the volume of work that is coming in.

Also, we recognized, in trying to determine the overall size of the program, the ANDA itself is the best indication of the workload as a driver. There are many other activities, some that you've already heard about, that Ted Sherwood detailed; some that you'll hear about when they talk about facilities that go on in the program that are beyond or not linked just to the ANDA itself, but it really is a program that the ANDA itself is the best indication and the driver of overall workload.

So at this point in the program and separately from the negotiations, there have been some coverage about the number of resources FDA is currently utilizing on behalf of the program. In the first two years of the program, we were building up that program and hiring new staff.

Page 71

There were over 1,000 staff hired during GDUFA I. It takes some time with federal hiring to get all of those new staff on board and even a little bit more for them to be productive.

In FY15 -- and this is in the GDUFA financial report for that fiscal year -- you can see that the program passes kind of a tipping point, where it begins to spend even more than it's collecting in one year. That's a common occurrence that happens in new federal programs. And currently, we are on track to spend over $400 million at our current work rate. And that is not an overspend per se, but it is a spend that is commensurate with the workload that we have and with the desire to continue to work through that pre-GDUFA backlog that we started GDUFA I with.

As has been mentioned earlier, we have met and exceeded those goals, and we have met the original backlog goal of making one touch, but the agency and the program are really committed to working through that and getting really those applications not just the one touch that they need,

Page 72

but all of the review work to get them approved and out on the market. So all of those factors informed our current sizing for GDUFA II, as well as the new negotiated commitments that you've heard about.

The final price tag that we arrived at is 493.6 million. That is a substantial increase over GDUFA I, which with, I believe, the collections we started at 299 million. But they're higher of course because of inflation, but that is still a substantial increase. But that is an increase based upon both the new program enhancements that we are putting into the program, but more importantly, it's really for the volume of the ANDAs that are coming into the agency. And in many ways, the best way to view that is a problem of success. The U.S. healthcare market needs a robust generic drug industry, and the ANDAs are the expression of that.

During the course of this, with this increase amount of funds, the agency probably will not be hiring significant new staff, but we will be

Page 73

working with staff that we have very hard. You will see over the next couple of years as we move into GDUFA II that output, as Ted Sherwood noted, is going to continue to increase, and we hope fervently that the number of review cycles to approval are going to decrease.

So let's talk a little bit about some of the most important modifications to the user-fee structure and how we arrived at this. One of the most important things in administering a user fee on behalf of the agency is to have some stability for the revenue stream, And to do that, you need to find a balance between application fees and some other type of fee.

In GDUFA I, that was the facility fee, which really was the one annualized fee. So facilities paid that fee every single year, whereas application fees are when a sponsor was following that application. And really to be stable, you want something that is more predictable. And the concept of a program fee, which is now being used in other user-fee programs as well, was considered

Page 74

and then adopted for GDUFA II for the proposal.

The application volume of course can fluctuate. We've seen it go up. But it has varied fairly dramatically, and this can pose challenges for the fees that are collected and for even setting and calculating those fees. So to better align with the program -- because the work does not stop in the generic's program just with the approval of an ANDA; that continues.

An ANDA really should be seen, especially when it's actively being marketed, as a live thing that may have updates and other things, inspections; surveillance inspections continue on manufacturing sites. So this is a new concept that really we think better reflects the program itself.

A few other things, we introduced, in addition -- the important thing on this annualized fee is now not only will facilities pay this annualized fee, but ANDA holders, so the sponsors themselves will pay an annualized fee because in the generic drug marketplace, it's often the case that not every individual approved ANDA is actually

Page 75

marketed or may not be marketed on a continual basis by that sponsor.

You'll see as we go through this that ANDA sponsors will be grouped into tiers based upon the size of their entire portfolio as opposed to a per ANDA fee assessed, which would have been one way to do this. There are multiple different ways of doing this, and in our negotiations with industry, we reached an agreement that the best possible way to do this is to think about it as an ANDA sponsor's total portfolio size. And I'll talk about this a little bit more in a moment.

As soon as a new ANDA holder has even one approved ANDA in their portfolio, they will move into this category of paying a program fee. If they do not have -- if it's a new ANDA holder who is new to the generic drug space, they will not begin paying this fee until that time. So all they would pay is actually the filing fee with ANDA.

A few other important changes to the fee structure. First of all, facility fees. The facilities will continue, both API and finished

Page 76

dosage form, to pay an annualized fee just as they did under GDUFA I. Percentages do change here. In the facilities, however, a couple of important changes are, one, facilities that do both operations -- this is not the majority of facilities, but there are an important number of facilities that do both of those -- will only pay one fee, and they'll pay the finished dosage form fee. So they won't be hit twice.

Another important change here is that contract manufacturing organizations, or CMOs, will pay one-third of the total of the FDF fee. This was an important change noted because contract manufacturers, which are defined in the statute, are those manufacturers who are also not the ANDA holder.

The generic drug industry, as Rob Berlin mentioned in his overview that we did for the negotiation, this is a very complex industry with a lot of different business models. You have some firms that are only ANDA holders, some firms that are only in the manufacturing space, and some that

Page 77

do a mix of both. So some of the changes to the fee structure are designed to more mimic the wide variety that we see in this industry.

A few other things that we decided to do, some of these mapped to the fact that we went with a program fee for ANDA holders. We've eliminated the supplement fees. Previously, industry was paying a separate fee for every time a prior approval supplement was sent into the agency. This meant a lot of very small fees coming in. This too can vary quite a bit, and really, it should be considered as part of the ongoing maintenance and life cycle of an approved ANDA.

This is also important, we feel, for purposes of encouraging updates by the industry. If industry does not have to pay every individual time that they want to make a small change, either for labeling, about other important safety updates, and some of those changes may even be requested by the agency itself, then we are much more likely to be able to facilitate that if they're not actually having to pay each individual time and it's more

Page 78

rolled in, at least conceptually, with the ANDA holder fee.

So we've talked a little bit about small business considerations, and a few important things that we have done to build into what was billed as a small business consideration, but in fact really was a much broader conversation based in the research work that was done and really from the conversations that we had with industry, and designing a system that more accurately reflected this industry, its complexity, and their ability, and really what they gain as value and benefit from the program.

The first thing that's important to note, no facility or an ANDA sponsor is charged this annualized fee until an ANDA in which it's listed has actually been approved. We think this is important not only because the approved ANDA is an important marker of their value and the revenue that they're going to be able to gain and the benefits that they see from the program, it's also important because, we believe, that by not doing

Page 79

this, we have removed at least a perceived, if not actual, barrier of entry into the generic drug marketplace.

Previously, if a manufacturer wanted to enter this space and was new into the space and listed in an ANDA, they might find themselves paying the facility fee for however long it took for that ANDA to actually be approved. With this change under GDUFA II, that will no longer be the case.

The annual program fee for the ANDA holder in the proposal has three separate tiers that is also designed to reflect new entrance into the generic drug space, and then to reflect the wide variety in size of firms that are engaged in this, so that we have a small tier for ANDA holders who have 1 to 5, a medium size for those once they reach 6 approved ANDAs up to 19, and then a large at 20-plus ANDAs.

There are a large number of ANDA holders, and Donal Parks is going to talk a little bit more about our initial thinking and some steps we're

Page 80

going to take to get our arms around this. But we reached these cut-off points with a lot of business intelligence and really driven primarily by our industry colleagues who know their own industry far better than we do by combining our resources and intelligence there. And I've already mentioned the CMO change in there. But CMOs are often smaller businesses than the individual facilities that might be owned by a much larger company.

Donal, I'm going to let you come up. Donal Parks from our Office of Management is going to talk a little bit about the ANDA holder fee, which is probably the most complex of our new fees.

MR. PARKS: Thanks, Mary Beth.

So as Mary Beth mentioned, we're going to have this new fee, so we've been thinking through how we're going to operationalize this. And it's important to note that companies may have affiliates and they may have approved ANDAs under different names in our system, and it wouldn't really be right to charge separate fees to all of them. We'd be fine with that, but you all probably

Page 81

wouldn't like it.
So what we're going to do is a clean-up effort so that we know who is related to whom, who should be showing up as one entity instead of several, and to do some data clean-up as well because in some cases, we have a company showing up with a comma LLC, and some with no comma LLC, and things like that.
So what we're going to do is go through a process of cleaning up, or allowing you to help us clean up, the data so that when the fees become due in October of 2017, it's seen as a reasonable approach.
Working through the timeline here, we have to publish the fees for FY18 in August of 2017. That's about two months before the fiscal year. So in order to do that, we're going to be posting information on our website and accepting feedback from folks who have an interest in it.
So starting around December, early December, we're going to publish a list of what our systems reflect as approved ANDAs. And what that list is

Page 82

going to show is the name of the owner of record, according to our system, the approved ANDA number, and the drug substance that it relates to.
That information will be available from our website on or around early December of 2016. And then that will give folks who are on that list an opportunity to check it out, and you'll be able to see if we're showing you as different entities, or you may have some sort of a corporate family that you want to reflect under one group.
What you'd be able to do is tell us, hey, I want to combine all of these under one. These are the ANDAs I'm claiming for my family. And then we'll take that information and clean up our database, and then we'll republish the list somewhere around March, early March or mid March, then that will hopefully show fairly well what those changes have been.
There will be changes. There will be mistakes. People can continue to send information back into us. And then around June, we will use the information we have at that point to help us

Page 83

establish the fees. We'll create the denominators, or calculate the denominators, send that off to the Office of Financial Management. They'll do the math. They'll publish the FR notice. In early August, we'll have the numbers.
Just as a summary to compare GDUFA I to GDUFA II, the column on the left shows the types of fees; the middle column, GDUFA I; the last column on the right, GDUFA II. You'll see that the percentage for the ANDA application fee is going from 24 percent to 33. The DMF is dropping from the 6 percent that was under GDUFA I to 5 percent under GDUFA II. Then for the annual fees themselves, the API and FDF facilities are going from 14 percent to 7 percent, and 56 percent to 20 percent, respectively.
The CMO facility that Mary Beth talked about is kicking in. That wasn't a differentiating factor in GDUFA I, but in GDUFA II, they will pay one-third of the FDF facility. So it will be one-third of the facility fee for either domestic or foreign. So foreign firms will still have the

Page 84

$15,000 foreign facility fee differential, so the CMOs would pay their one-third fee plus that as well.
The holders did not have a separate fee under GDUFA I, but under GDUFA II we will, and that will account for 35 percent of the total target revenue every year, and it will be spread out as follows. The small group, the 1 to 5 ANDA holders, will pay one-tenth of the large fee; the medium, those with 6 to 19 approved ANDAs, will pay four-tenths or 40 percent of that large fee; and then the large, the 20-plus holders, will pay the full fee. When we set the fees in August of 2017, you'll see what the fees are.
I'm going to turn it back to Mary Beth for this other stuff that I don't understand.
MS. CLARKE: You've heard quite a bit about GDUFA I transforming the generics program and this deep foundational restructuring. And that deep foundational restructuring really goes beyond just the ANDA review process. We want to talk just a few minutes about some important enhancements,

Page 85

which are proposed accountability in reporting enhancements that go in.

These are all part of moving the generics program into what I'll call its final phase of really being managed, measured, and reported out as a program much more similar to the new drugs or any of our other user-fee programs. We have built in some things into the commitment letter that provide a much more robust internal capacity development here within the agency, which will allow for regular performance monitoring and reporting out. So there will be a much more frequent regular assessment of the progress towards the goals.

The original statute called for annual reporting, and that has been already transformed and is done more frequently. But there are quite a number of things within the commitment letter that outline additional reporting responsibilities, and there are resources going to a much more robust capacity and workload analysis that we'll be doing, much more consistent methodologies, which include the reporting of all of the metrics and about the

Page 86

use of the resources and the administration of the program overall. And this will be on a very similar basis and platform with the other user-fee programs that the agency is administering, particularly those in the drugs area.

We also have built in third-party evaluations that we'll be doing. We really will work on a series of activities to have a much more, as I mentioned, robust resource management planning and modernized time reporting system that will more accurately reflect, in a much more detailed level, all the different component parts of the program and what the resource utilization is to achieve the performance goals that have been negotiated.

It also involves an independent third-party evaluation of the program, so not all of this will be in-house. We'll have an ongoing in-house effort, but we will have an outside assessor doing that as well. And we will have a formal public report, which will be published upon then, with recommendations no doubt because there always are.

So the agency, not only in GDUFA but in the

Page 87

other programs, but most importantly for this program now, is really committed to the financial administration of the program and to enhancing its overall fiscal responsibility in the program. This is particularly important for us because we have multiple user-fee programs, as many of you all know, right now.

So we are managing multiple streams of money, and all of them come with very specific performance goals. So this is a commitment that really -- GDUFA is part of a larger strategy on behalf of the agency to make sure that this is managed at an appropriate level.

Some of the reporting that you can look for under GDUFA II -- you will see some monthly reporting on performance, additional quarterly reporting that will be ongoing, and of course the annual report, which currently exists. This is going to allow industry and other stakeholders -- and we certainly have seen, during the course of GDUFA I and through this negotiation process, that we have a lot more stakeholders

Page 88

beyond industry itself: the public, consumer and patient organizations, and Congress itself. So this will give all stakeholders more regular information about how the program is progressing.

I'd like to stop now. We haven't had too many questions, and we do have the open comment period at the end. But fees have a tendency to generate a lot of questions, so I'd like to open up the floor in case there are some questions because this we understand is a bit of a fast and high-level overview.

(No response.)

MS. CLARKE: Any comments from anybody else that I missed?

(No response.)

MS. CLARKE: No? All right. Well, that's really good.

We are then at a break. We are ahead of our schedule. It is now 11:00. Some of our panelists for the third and final panel are in other meeting obligations right now. So I think what we are going to do is take an early break for lunch, and

Page 89

then try to reconvene shortly after 12 noon. If I could ask folks to be back at 12:15, which is a little ahead of our start on the agenda. There is the small cafe here in the lobby, which is available for folks if they want to have lunch in that interim time period. Thank you.

(Whereupon, at 11:06 a.m., a lunch recess was taken.)

Page 90

A F T E R N O O N S E S S I O N

(12:46 p.m.)

Panel 3

MS. CLARKE: If I can ask folks to take their seats, we're going to resume with our third panel, focusing on facilities. We have our same, three industry trade representatives here, and for FDA, we have Ashley Boam and Ann Marie Montemurro.

Ashley, are you starting off?

MS. BOAM: Yes. Thank you, Mary Beth.

An important part of the proposed agreement has to do with certain enhancements in the area of facilities. Just as a little bit of background, FDASIA, which was promulgated into law in 2012, changed how FDA was instructed to do our surveillance inspections. And in particular, the law eliminated a prior requirement to do inspections, surveillance inspections, on a certain frequency. Instead, the law directed FDA to do our drug inspections across the globe on the basis of risk.

However, the transition to this new

Page 91

paradigm, we heard from our industry counterparts, has been commercially disruptive, in part because those prior expectations and requirements for certain frequency-based timing of inspections had provided certain predictability for the industry.

So while we recognize a facility assessment is not limited to the ANDA program and to GDUFA, we did include in GDUFA II a number of facility related enhancements to try to address some of the challenges raised specifically by the generic drug industry.

In particular, the enhancements to address concerns raised by some of our U.S. API manufacturers, to mitigate certain export related challenges that were identified by this group, in the proposed commitment letter, FDA would issue a guidance to explain our new risk-based site selection model that we have been using since the Act directed us to in 2012; how that works, how we use that to prioritize facilities for surveillance inspections.

We would also undertake certain outreach

Page 92

activities to foreign regulators to help them understand how FDA operates its site selection model, and then to support the export of safe and effective pharmaceutical products by the U.S. based pharmaceutical industry in several ways, including communications to provide the current compliant status of U.S. facilities to our foreign regulator counterparts.

On the ANDA side, the application holder side, to address some of the concerns that we heard about -- transparency and the speed of facility assessment and the potential impact of that facility assessment in a surveillance mode against an application that happened to be in-house, and the potential impact on approvability and product launch -- FDA would communicate to an applicant when we've identified facility issues from an inspection that could impact the approvability of the ANDA or an associated post-approval supplement.

We would communicate that through an IR, which is an information request, a discipline review letter, or a complete response letter, as

appropriate, given some of the other circumstances with the application.

We would also communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection. So if FDA has reviewed all the information from the inspection and new follow-up information from the facility, and has determined that there are not issues that would hold up approvability of any associated application, that would be made clearly known within 90 days or the end of that inspection.

As we go forward, we'll also provide updates to the industry and seek stakeholder feedback on how this process is running and to make sure that we're addressing some of the concerns that arose in GDUFA I as we move forward with GDUFA II.

In addition to providing enhanced transparency about the compliance status of GDUFA self-identified facilities and sites, we would update our existing publicly available database on

a more routine basis, and include not just manufacturing facilities but sites that are involved in the conduct or analysis of bioanalytical or clinical bioequivalence or bioavailability studies.

The proposed commitment letter also includes certain enhancements related to the Drug Master File program, so there are a number of targeted improvements to the DMF review process. To begin, DMF review comments that were sent to the DMF holder would be issued at least in parallel with the issuance of review comments related to the DMF for the ANDA.

We would also outline procedures and timelines for telecons or email exchange as desired by the DMF holder to clarify first-cycle review deficiencies identified by the agency in the hopes that clarifying how these exchanges can occur will get us to an acceptable DMF status more quickly.

Then once we have done a complete review for the DMF and there are no open issues related to that DMF for the ANDA that references that DMF, FDA

would issue a first-adequate letter. Once the DMF has undergone a complete review and the ANDA referencing it has also been approved, or tentatively approved, FDA would issue a no further comment letter, meaning there are no additional questions to that DMF.

By fiscal year 2019, FDA would issue a guidance on post-approval changes to a type 2 DMF, as well as to address the appropriate submission mechanisms for any ANDAs that reference that DMF for which post-approval changes are occurring.

That concludes my review of facilities and DMF enhancements, and I'm happy to entertain any questions.

(No response.)

MS. BOAM: Thank you.

Open Public Comment

MS. CLARKE: We are ready to begin now our open public comment period, and we have one registered speaker I know of, who I will introduce and ask to come forward, which is Paul Brown with the National Center for Health Research. If you

can come forward to the microphone.

MR. BROWN: Good afternoon. I'm Paul Brown. I'm the government relations manager for the National Center for Health Research. Thank you for the opportunity to speak on the commitment letter. Our center is a think tank in Washington, D.C. We conduct and scrutinize research on the safety and effectiveness of medical products. We do not accept funding from pharmaceutical companies. We do not have any conflicts of interest.

We respect the FDA, and we're committed to ensuring that it has the resources it needs to make sure that our medical products are safe and effective. Given the inadequate appropriations provided to the FDA, we strongly support increasing GDUFA and other user fees to improve FDA's resources in order to enable the agency to fulfill its public health mission.

Our center has attended all of the GDUFA II meetings, either in person or by phone. We agree with GDUFA's intent, which is to provide additional revenues so that FDA can hire more staff to improve

Page 97

the generic drug review process that will lead to increased access to generic drugs, which is, as mentioned earlier today by several people, saving trillions, nearly $1.7 trillion or less. We also support the commitment letter's streamlining of the user-fee structure, which will provide a more stable resource of funding and give small companies a financial break on user fees.

We support the GDUFA II agreement because it increases user fees by nearly $1 billion over five years. Increased fees are needed because the number of abbreviated new drug applications was underestimated previously, as was already mentioned. However, we are concerned that if the applications go up more than estimated in GDUFA II, then even the increased user-fee amounts will not be enough to cover the needed FDA staff.

We're also concerned that fees may not have increased enough to offset the increased workload that the performance goals require FDA to meet. The performance goals are resource-intensive and include tight timelines for review of original

Page 98

ANDAs and ANDA amendments, PAS's and PAS amendments. They also include short timelines regarding the review of drug master files, controlled correspondence, pre-submission meetings, safety determination letters, teleconferences, or T-cons as you've been referring to them today, and many other deadlines.

Some of the performance goals in the commitment letter seem a little unrealistic. For example, a commitment letter states that FDA will meet 90 percent of most performance goals by certain dates, including six months for priority major ANDA amendments. That sounds like a New Year's resolution to me; I will lose 90 percent of my body fat by June. It's a nice goal, but I'm not sure it's actually doable.

As public health advocates, we need more information on how much time and staff it currently takes the FDA to review these applications, then we can better estimate how much additional staff and funding it will take to reach these goals.

I'm just going to talk briefly on a couple

Page 99

of things that aren't in the commitment letter.

Safety. FDA monitors the adverse events reports for generic drugs. This is important. It is not unusual for side effects from drugs to show up years after the drugs have been on the market when the generic drug is dominating the market or perhaps the only drug on the market. That is why GDUFA fees should be used for enhanced safety reviews.

Conflicts of interest. FDA's primary mission is to protect the public health. GDUFA and other user fees should fund an independent review not just of performance goals, but of how the program, the user-fee programs, have affected overall public health. Have user fees changed FDA's priorities? Is FDA now treating industry as a customer that needs to please instead of acting as a regulator to ensure the public health?

I just want to spend a couple seconds on process issues. Let's start with the positive. We greatly appreciated the GDUFA II fee structure summary. It was concise and easy to read. Thank

Page 100

you very much for putting that together.

Regarding the commitment letter itself, it could use some improvement. The current letter uses too much jargon. Too many abbreviations are not defined making the commitment letter a chore to read. I would suggest next time around when you're doing the outline, actually spell out what the abbreviation is like A, B, and C, and then start using the abbreviations.

Regarding the meetings themselves, FDA needs to somehow improve its outreach efforts. It was disappointing that few consumer, patient, and public health advocates attended the GDUFA stakeholder meetings.

For GDUFA III, we recommend that you hold some of the meetings in Washington, D.C. at the HHS building. It is actually very difficult for some folks to get out here to the White Oak campus. Metro is not very accessible for here. So I would suggest not having all the meetings there, but maybe every other meeting, or maybe every third meeting, in Washington, D.C.

Conclusions. We strongly support increasing GDUFA and other user fees to improve FDA's resources in order to enable the agency to fulfill its public health mission. We strongly support the increased resources for hiring review staff, however, we have not seen enough data in the commitment letter to convince us that the GDUFA user fees are adequate to cover the increased workload.

Patients, consumers, and public health advocates should have a greater role in the discussion of how user fees are spent. We do not pay the fees, but we do pay for the medications. We pay directly when we use our own money to buy the products. We pay for the insurance. We pay for public health programs. And we pay for health problems that may result when medicines don't work well. And as taxpayers, we pay for the appropriations that are still supporting major portions of FDA resources. We should be at the table, or at least in the room, when negotiations take place for user fees.

Thanks for the opportunity to speak, and I want to thank -- this is my last day at my current job. I've been doing this for eight years. I want to thank Mary Beth and Keith and others at the meetings. You've always held professional meetings, and I found them informative. Thank you.

Closing Remarks

MS. CLARKE: Thank you for your really comprehensive comments, which we will take under advisement, definitely. You covered quite a bit about the agreement, as well as the process, and we appreciate that.

Do we have anybody else here in the audience who would like to make a statement on behalf of the public?

(No response.)

MS. CLARKE: For those of you all who are watching or joining us remotely, we don't have an ability to have you ask questions right now or make comments live, but we do welcome your comments in written form to the docket, which is open, as we've said a few times, until November 16th. So please,

we would really appreciate that. The link to the docket is directly in the Federal Register notice, which is displaying today.

If we have no further either statements for the record or any other questions, then we are adjourned for today. Thank you very much for your input and for your interest. We look forward to hearing more from you before November 16th. Thank you.

(Whereupon, at 12:34 p.m., the meeting was adjourned.)

B

D

E

F

G

H

N

O

P

Q

T