FINAL ASSESSMENT OF THE PROGRAM

FOR ENHANCED REVIEW TRANSPARENCY

AND COMMUNICATION IN PDUFA V

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P R O C E E D I N G S

(11:01 a.m.)

Welcome

MS. HAFIZ: Hello, and good morning. Welcome to the public meeting on the final assessment of the program for Enhanced Review in Transparency and Communication in PDUFA V.

My name is Azada Hafiz, from the Office of Strategic Programs in the Center for Drug Evaluation and Research, and I will be your moderator today.

In today's meeting, the independent contractor will discuss the findings of the final assessment, and public stakeholders will have an opportunity to present their views on the program.

I do want to mention that in addition to this meeting, a docket will be open until next Monday, April 3rd, to which the public may submit comments regarding their perspectives on the final assessment.

The agenda for today's meeting is Valerie Overton, the vice-president of ERG Eastern Research Group; the independent contractor who conducted the program evaluation will present the final assessment.

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We will then have panels composed of FDA staff and industry stakeholders who will provide their experience and perspectives on the program. We will start with FDA panelists and then transition to the industry stakeholder panelists.

After the panelists, we'll have time for public comments, and you can sign up at the registration table right outside if you would like to provide a public comment.

Before I hand it over to Valerie, just a reminder that the restrooms are located in the hallway on the right side of this room. Now, I'll turn it over to Valerie. Thank you.

Presentation of the Final Assessment

MS. OVERTON: All right. Thank you very much. As Azada said, my name is Valerie Overton. I'm with Eastern Research Group, the independent contractor who conducted the evaluation of the FDA's program for NME NDAs and the PDUFA V.

What I'll be doing first is to just provide a little bit of background and introduction and then go over some highlights of our results of the evaluation,

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answer the assessment questions, and talk about our findings and recommendations.

To start, what we were charged with doing was to look at every NME NDA and original BLA with the first-cycle action in PDUFA V. The scope of the program compasses all of that. We looked at every application that went through the program, up through our cut-off date for the evaluation.

The program includes some major attributes such as mid-cycle communication, late-cycle meeting, a review clock that begins on the 60-day filing date.

The goals of the programs were really to improve communication between applicants and FDA review teams, to improve the transparency of reviews, and to improve the efficiency and effectiveness of reviews.

If all of those things happen, then one would expect that there would be a smaller number of review cycles to get to the point of approval for where that's warranted based on the efficacy and safety of the product being reviewed.

Our program evaluation was something that was a commitment made for PDUFA V. We were charged with

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identifying relationships between program attributes, review process attributes, and application attributes, and the first-cycle regulatory outcomes, and time to first-cycle regulatory outcomes.

We're looking at lots of different aspects of applications in the review process and seeing what that looks like in terms of first-cycle actions and the timing of the review. We were also charged with looking at how applicants and FDA staff characterize communication and application reviews in the program.

In order to accomplish this evaluation, we began with a set of assessment questions having to do with the goals we just described. We developed a set of detailed metrics and protocols and instruments in order to collect the data for those metrics.

We collected the data by observing meetings between FDA and applicants, by reviewing documentation, and by interviewing both applicants and FDA review teams separately after the first-cycle action has been taken.

We then looked at that data in terms of descriptive, statistical, and qualitative analyses, and

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developed a set of findings and recommendations.

Our interim report was after the first two years of the program, and that was published in March 2015. This final report was after roughly four years of the program and was published December 31st, 2016. That is the subject of this presentation.

The final report is online, on FDA's website. This is the table of contents, if you will, just a summary of what's in that report.

To start out with, in terms of the applications that we were looking at, we were comparing applications under PDUFA IV and PDUFA V for the program for NME NDAs and original BLAs.

All of the applications that we looked at were ones that have been filed and received the first-cycle action. In the program that totaled 171 applications; in the baseline, there's 219 applications.

Remember, there were more in the baseline because we were looking at all of PDUFA IV as opposed to just the first almost four years of the program. There are a greater number of applications in the baseline for that reason.

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When we look at what happened with all of those applications, we looked at, of course, the first-cycle approval rate, the number of complete responses, the number of withdrawals after filing to get our total numbers.

What we saw in the program was a statistically significantly higher first-cycle approval rate that was 79.5 percent on average over the course of the first roughly four years of program compared to 54.8 percent in PDUFA IV.

We also looked at the milestone communications I mentioned. The program instituted some requirements for the pre-submission meetings, some recommendations for the pre-submission meetings, and a mid-cycle communication, and a late-cycle meeting.

Given when they occur, the topics discussed are probably not too surprising. In the pre-submission meeting, the topics that are most frequently discussed were product quality, topline results and data, and the format and content of submission, what you would expect in the meeting before submission.

In the mid-cycle communication, the topics

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that were most frequently discussed were clinical, product quality, and then a bunch of other topics including labeling, PMR/PMC, a late-cycle meeting, safety, pediatrics, REMS, and so forth.

In the late-cycle meeting, the topics that were most frequently discussed were review issues, and labeling, and PMRs and PMCs. Those really reflect what you would expect based on the timing of those meetings throughout the review cycle.

Based on our observations of these meetings and also results from the interviews with both applicants and FDA staff, we heard frequently that the value of the communication was seen as quite high.

The applications especially appreciated the open and early communication from the pre-submission meeting through the mid-cycle communication and the ongoing open communication through the late-cycle meeting.

There was a lot of benefit perceived by the applicants who we interviewed in terms of the discussions of the understanding of what the expectations were for submission in the pre-submission

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meeting and the assessment of the readiness to submit in the pre-submission meeting.

Then in the milestone meetings, during the review itself, again, the open communication and especially developing that shared understanding of the progress and potential issues so that the review itself, and the progress, and the issues have a high level of transparency associated with them. Because of that, there was an opportunity to work and to understand the issues and work to resolve them where possible.

As I mentioned, the first-cycle approval rate was higher in the program than in the baseline. If you look at all applications, only priority applications, or only standard applications, in all three cases, the first-cycle approval rate is higher in the program than in the baseline. Those differences were statistically significant.

In terms of what applications were most likely to receive first-cycle approvals, we found that those aimed at unmet medical needs, tended to have higher first-cycle approval rates than others.

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Those with priority review tended to have higher approval rate. The other category that had a higher approval rate were those with major amendments and goal extensions.

In the program, the expectation is that there would be a goal extension when there was an opportunity to -- hopefully, an opportunity to address and resolve issues in time for a first-cycle approval with an extended PDUFA goal date. Indeed, we did find that in those situations, there was a higher approval rate.

In terms of applications with lower approval rates, these aren't really a surprise either when there's a longer-than-average primary review time, one or more significant issues identified at the mid-cycle communication, and at the late-cycle meeting.

All of those three characteristics have to do with applications that just have more challenges. There are more issues; they're more problematic, and so those tended to have a longer primary review time as a result and also, a lower approved first-cycle approval rate.

In terms of time to first-cycle action, as

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expected, the median time to first-cycle action was longer in the program than in the baseline. There is a two-month difference because of the review period starting 60 days from the receipt.

Accordingly, in general, the time to first-cycle action, whether it's approval or otherwise, was roughly two months longer in the program than in the baseline.

Patterns, in terms of time to approval, so the main patterns had to do with, on the one hand, prioritization of the application. Applications that had special designations such as priority review, a breakthrough therapy designation, and so forth, those kinds of prioritized applications tended to have a shorter review than those applications that did not have special designations.

In terms of applications that had a longer time to approval, again, as one would expect, they would be applications that did have goal extensions because that extends the review clock, a longer than average primary review time, and one or more deficiencies identified at the late-cycle meeting.

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Those are situations where the full review clock was needed in order to look at the application.

I mentioned special designations, and so I just wanted to cover that a little bit more. There were relatively high first-cycle approval rates and relatively short time to approval for applications with special designations.

Here, you see various groups of program applications with just a selected sampling of special designations compared to all program applications as a whole.

You see that a higher proportion of those applications with special designations had first-cycle approval rate, had shorter time to first-cycle approval, and of course, those are the ones that generally received priority review as well.

I also mentioned goal extensions. In the program, as I mentioned, the expectation was that the goal extensions would be issued primarily when there was an opportunity to then resolve any remaining issues and achieve a first-cycle approval where warranted, where the application showed sufficient efficacy and

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safety.

With that as an expectation, we did indeed see that applications that received a goal extension were more likely to receive first-cycle approval, and that was certainly true in the program as compared to the baseline which is PDUFA IV.

Similarly, the time after the original submission of the goal extension was issued was much more variable in the program than in the baseline because in the program, there was the opportunity to issue a goal extension really at any time during the review. You see a broader range of times for when the goal extension was issued in the program than it did in the baseline.

All right. Inspections. So in the PDUFA V program guidelines, the expectation for applications in the program is for inspections to be completed within six months of receipt for priority applications and within ten months of receipt for standard applications.

There are a lot of different ways to think about inspections. There is the actual conduct of the inspections themselves at the facility, there is the

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process of resolving issues that are identified, and then the final recommendation about the acceptability of the sites.

For the purpose of this evaluation, inspection completion was defined as the last overall site acceptability recommendation for CDER and the latest GMP or GCP site inspection date for CBER. The reason why it's different between CDER and CBER is because the data that were available to us were different.

I just want to illustrate what that means in terms of what we're looking at in terms of timing for when we define inspection completion this way. For the inspection process, first, of course, there is the planning preparation phase where FDA is looking at a site list submitted with the application, evaluating what sites need to be inspected, scheduling and coordinating involved in that kind of preparation that happens.

That usually happens in the first few months after receipt and can extend later if more site inspections were needed because sometimes during the course of review, additional inspections, additional

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sites come up that are found to need inspection that was not clearly laid out initially in the application.

After that planning and preparation phase, there is the actual conduct of the inspections at the sites. Those usually take place between months four and eight and again, can extend later if more site inspections were needed either because new sites were found or because it turns out that a site needs to be re-inspected.

Then the next things, and these are all overlapping phases as you can see because the variability in terms of the number and location of inspections, when it's determined that sites need to be inspected, whether the inspections aren't needed, and so forth.

The next phase is the resolution of any issues that are identified during the inspection. That is extremely variable in duration depending on the number and severity of issues.

The goal is to resolve all of those issues in order to achieve approvability. Of course, that doesn't always happen, but that is the goal of this

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phase of the inspections process.

Then, there is the kind of final stage of the inspection process which is preparing the overall site recommendation and decision. Again, when that happens, it's extremely variable depending on all of the factors I mentioned with the number and location of the sites that need to be inspected, for example, whether if there's just one or two, whether they're in the United States versus in other countries, the number and severity of issues that are uncovered, whether additional sites need to be inspected, or whether a site needs to be re inspected, and so on, and so forth. That is an extremely variable period of time.

In some cases, there's also multiple site recommendation dates because there is an initial site recommendation date, and then further activity happens, and then there is a second site recommendation.

In this process, the last date here, the recommendation and decision date, is the one that we used for inspection completion in CDER. For CBER, it was the date of the last site inspection, so earlier in the process.

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That is going to be important because what we saw, of course, using these different definitions, is that the CBER sites tended to be completed earlier than the CDER sites because of that difference in definition.

Here, what I'm showing you is a distribution of the inspection completion dates for the applications in the program. This is just the site completion, that earlier phase before all the resolution has happened and before there's been a recommendation on the site.

You can see that the bulk of the sites are inspected between months four and eight, with some occurring earlier or later, depending on review priority or whether there were additional sites that needed to be inspected, or whether there was a goal extension, and so some of the inspections took place later than was typical.

Here, I've added on the recommendation date, the last recommendation date. Here, you can see in the blue, again, the site completion dates; and in the red, you see the recommendation dates.

Again, the inspections themselves typically

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took place between months four and eight. The recommendations typically took place months five and twelve, depending on the whole range of factors that I mentioned.

In terms of what we found, there's another wrinkle that we wanted to mention in terms of providing context for the inspection results. At the time of the interim report, there had been one process and managing structure in place for inspections.

Just after the interim report was published, FDA transitioned to a different structure for managing the inspection process. Management of CDER's pre-approval inspection process responsibilities were consolidated under the Office of Pharmaceutical Quality, OPQ.

So is the case (ph) after that transition that ORA leads and conducts most pre-approval inspections performed for NME NDAs, but OPQ performed the initial facility evaluation, participates in some pre-approval inspections, and makes the final facility recommendation.

The reason why I bring this up is that this

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occurred kind of midway through the program. We would expect that there would be some observations around that in terms of what we saw with the inspections. Whether that changed the results or not, that's just an important change to note as context for our results.

What we noted starting with the interim report was that historically, it was challenging for FDA reviewers and applicants to know the status of inspections. That was one of the findings that we found in the interim report.

Given this transition that took place kind of midway through the program, there was kind of the first couple of years with the old management of the inspection process and then a transition period where applications were now the responsibilities for CDER and the NDAs. It was consolidated under OPQ, and there was some transition period for that. Then after that, things settled in place in terms of OPQ overseeing the inspections process.

After the transition period, we haven't had a long enough period of experience with those applications that had inspections after the transition

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period was complete in order to make any firm conclusions about changes in transparency, communication, and so on, and so forth as of the cut-off for the final report, which was June 2016.

The program evaluation completion target were met for 46 percent of program applications. Again, when I doggedly went through those slides about how we are defining inspection completion for the purpose of the program evaluation is for the bulk of applications for CDER applications -- that last recommendation date. That last recommendation date includes all of the time that we spend resolving -- of course, after all the time spend resolving issues.

That last recommendation date, over 50 percent of the time occurred after the target of six months or ten months depending on the application receipt, depending on whether it was standard or priority.

There are a lot of reasons for that. The reasons for the final recommendation happening later in the process include situations where there were enough issues that needed to be resolved, that they couldn't be resolved by that six- or ten-month date, that there

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was continuing efforts to resolve those issues after that time so that there could get to a point of approvability in time for first-cycle review.

In some cases, the reason for that was the need for more inspections late in the process and as I mentioned, attempt to achieve acceptability in time for first-cycle approval. There are a whole bunch of reasons why the completion target date was only met roughly 50 percent of the time.

I could go on and on about this because it's easy to look at that number and think, that looks pretty bad. When you look at what's going on during that time, what we heard, what we observed, what we heard from FDA staff in interviews, what we heard from applicant in interviews suggests that that is a very productive time to resolve issues.

That late date is not necessarily a bad thing; often, it's a good thing because if you had to do the site recommendation by that six-month or ten-month, you would more often have to recommend against approval whereas continuing to work after that date, then they (inaudible) to work to happen to resolve issues so that

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there could be approval.

Complete response letters, I mentioned that the first-cycle approval rate is high in the program, has been high in the program which means that the CR rate is low. The number of CR letters is relatively small compared to the baseline.

What we see here are what the top three issues that are cited in complete response letters: efficacy, product quality, and safety. For the most part, there's not a big difference between the issues that are cited in the program, the CR letters in the program versus in the baseline.

The exception to that is that safety is more often cited in CR letters in the program than in the baseline than in the program. I would just caution, again, that the numbers are small, and so I would be hesitant to read too much into those numbers. They're certainly not statistically significant, given the small numbers.

Time to resubmission, once an application had been CR'd, then there's the opportunity to resubmit. Given that the program is still continuing through this

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time, there hasn't been a lot of time for applications that receive a CR to resubmit and then have a second-cycle action. The sample size is too small for a statistical analysis at this time.

As of the cut-off analysis for the final report, there had been 11 program applications resubmitted, compared to 65 applications resubmitted from the baseline, from PDUFA IV. Again, remembering that the two reasons for that is one, there were smaller proportion of applications that received a CR to begin with and then not as much time has elapsed for a significant number of resubmissions to take place; whereas with PDUFA IV, there's been all of these years since then for a resubmission to take place. Those are highlights of the results.

Now, what I'm going to do is to look at the evaluation questions or assessment questions that were laid out for this evaluation.

The first pair of questions has to do with: What is the relationship between program attributes and first-cycle outcomes? What is the relationship between program attributes and time to first-cycle outcome?

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As I mentioned, that relationship between program attributes and first-cycle regulatory outcomes, for the program as a whole, is that the first-cycle approval rate was statistically significant and higher in the program than in the baseline.

For time to first-cycle outcome, the first-cycle reviews took longer in the program than in the baseline as expected. Nevertheless, in interviews with applicants, they still -- despite that difference, still view the program as having value in enhancing review transparency, communication, predictability, and efficiency.

In the interviews with applicants, there was still a positive perception of the program regardless of the time that it took to get to first-cycle outcome.

The second pair of questions has to do with: What's the relationship between review process attributes and first-cycle outcome, and time to first-cycle outcome?

Review process attributes, we looked at the priority of review, major amendments, and a whole bunch of other metrics. These are examples of metrics that

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stood out.

Two attributes were associated with higher first-cycle approval rates, priority review, and the goal extension as I mentioned. One attribute was associated with the lower first-cycle approval rate, that being a longer time to primary review completion.

What I would just remind you of with that one is that the longer time to primary review completion tended to be associated with applications that had more issues. It's not that FDA was taking longer for the same quality application; it had to do with applications that had more -- so it's really a circuit for applications that had more issues.

In terms of time to first-cycle outcome, the two attributes that were associated with longer meeting time to first-cycle approval was, again, the longer time to primary review completion and of course, having the goal extension which extends the review clock.

The next pair of questions has to do with the relationship between application attributes, and first-cycle outcomes, and time to first-cycle outcome. What we saw with the applications is that applications that

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had the highest first-cycle approval rates tended to be those that addressed an unmet medical need and therefore had priority review.

The shorter time to first-cycle approval tended to be the same applications. Again, those have been a priority review which is expected because, of course, there's a shorter clock with priority review reviews.

The last couple of questions have to do with how applicants and FDA staff characterized the program. This slide has to do with how they characterize enhanced communication under the program.

In interviews with applicants and review staff, separately, the characterization of program communications was largely positive. Interviewees typically stated that the communication was excellent and constructive.

They commented that the milestone communications facilitate a more holistic discussion with the application, provides for a broader FDA input, provides for a greater understanding of each party's perspectives, and provided a more efficient means of

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resolving questions and issues. The review staff, similarly, described the communications under the program as constructive.

One thing that I wanted to mention here in terms of the applicants' characterizations of the communication is many applicants went out of their way to describe the review staff, and especially the RPM, the regulatory project manager, as being very responsive, constructive, and flexible, and expressed a great deal of appreciation for the efforts of those FDA staff.

There had been comments, again, on an ongoing need to improve the transparency of the status and results of the inspections which I described earlier in terms of there being insufficient data since the transition to the new management structure has been fully implemented to really make any firm conclusions about that.

Again, how do applicants and FDA review staff characterize application reviews under the program? The last one had to do with communication. This has to do with the reviews themselves.

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Again, the characterizations of program reviews were largely positive. Folks commented that the reviews were very transparent, very predictable, very efficient, and that they were especially beneficial for applications that require substantive discussion and issue resolution throughout the review so that the additional communications provided a mechanism for doing that.

Review staff acknowledged that the additional program milestones added to the total amount of work that's required for any given review but that that additional burden is manageable.

A couple of years ago when we talked about the interim report, we communicated a set of findings and recommendations. The findings and recommendations for this final report are largely similar, except that we have removed a few of the findings and recommendations because of actions that FDA took midway through the program in order to respond to some of the issues that we identified at that time.

One had to do with mid-cycle communication procedures, having to do with good communication

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practices. Those have become pretty much universal in the program. That is no longer a finding or a recommendation that those have been proceeding smoothly.

The early involvement of a signatory authority is something that has been part of program expectations. Early in the program, we would say that for the most part, that was happening. There were some inconsistencies perceived on some people's part as to whether that was happening with every application. Since there have been reminders of that, the practice has been consistent with program expectations.

The other comment that we heard was that in some cases, FDA is making attempts -- or plans and attempts to approve applications even earlier than the PDUFA goal date.

With expedited reviews, when you have a shorter review timeframe, it can be difficult to accomplish all of the program requirements in that short timeframe.

In response to that, FDA provided refined guidelines for expedited reviews. What we have heard

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since then is that the refined guidelines have been helpful for keeping up with expedited reviews.

Now, I'll go into the findings and recommendations that stand for this final report. Overall, the program has been successful in enhancing review transparency and communication, so no recommendation needed.

Overall, the new program milestone communications have enhanced the predictability of reviews by serving as anchor points for applicant and FDA planning and work, and for providing a forum for holistic, multidisciplinary discussion of application status and paths forward to resolve approvability issues promptly, if possible. There's no action needed.

By providing more opportunity to identify, discuss, and resolve substantive issues during the review, the program has created conditions that enhance the ability of applicants and FDA reviewers to work toward application approval in the first-cycle where possible. This is especially true for applications with substantive but resolvable issues where a full

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review clock is needed. Again, it has been a positive finding for the program and no action is needed.

Program implementation has not been resource neutral. Implementation has increased the burden on FDA's primary reviewers, diverting effort from review work to meeting preparation, and sometimes resulting in a need for additional primary review addenda.

FDA review teams have been able to manage the burden but have noted that additional new burdens might, in some cases, introduce a risk of missed deadlines, compromise the thoroughness of reviews, and impact other non-program work.

I would stress, again, that as the situation stands, FDA staff have been saying that the extra burden is manageable at this point. This is really just a note. If and when new review process requirements are added that, of course, there would be a need to analyze the associated burden.

We note this, however, that that would be something that FDA would do in any case. It's not a recommendation that would be endorsed (ph) surprising. It would be something that FDA would do (inaudible).

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Regardless of sponsor size and experience, many sponsors need more guidance on the format and structure of an application to meet FDA expectations. In some cases, the sponsors have asked that this be done by review division or team and indication/therapeutic area.

Sometimes sponsors request additional Type C meetings months before the data-orientated pre-submission meeting in order to have greater understanding on format and structure expectations. Some review teams believe that the existing guidance should be sufficient and holding an earlier meeting without data is premature.

I think that what we hear from sponsors is that sometimes they would like to hear or receive more guidance. The goal here is really to evaluate options for when and how to communicate information about this format and structure of applications.

There are a lot of ways of accomplishing that. That could include providing internal reviewer aids, increased use of Type C written responses, and so forth to answer questions from the sponsors.

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Application orientation meetings. In certain CDER review divisions with priority applications where an early action is expected or desired, holding an application orientation meeting within a month or so of submissions has helped acquaint FDA disciplines with application datasets and establish early communication between applicants and FDA about review expectations and perspectives.

To date, application orientation meetings have been held under pre-specific circumstances. As I mentioned, when an early action is being planned, and it's essentially a priority application.

Some folks felt that there might be additional applications when an application orientation meeting might be useful as well. The recommendation here is to consider the value of providing information about application orientation meetings to FDA review teams, along with the option to conduct such meetings at the review team's discretion, especially for applications with special designations.

The application orientation meeting is not necessarily something that is required for every

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application, especially standard applications, but it's something to consider as an option where it might be beneficial to the review process. Our understanding is that FDA is proposing this option for PDUFA VI.

There is a high volume of information request during reviews. What we heard from applicants and review teams is that providing target dates for responses is good practice and that applicants would also benefit from receiving confirmation that the responses are complete.

The first part of the recommendation is to adopt inclusion of target dates for information request responses as a good practice, which we do see many reviewers doing.

Second, to develop a simple optional approach for tracking information requests and amendments that can be shared between review teams and applicants.

One thing that I would note here is that it can be a little bit complicated in terms of describing when a response to information request is satisfactory versus complete because simply responding, providing information in response to an information request might

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or might not close out that information request in terms of what FDA needs. There might be further questions, further issues, and so forth.

If FDA and applicants can pursue this option, it needs to be clear that by confirming receipt or affirming the completeness of the information for that particular FDA information request to applicants doesn't necessarily mean that that issue has been resolved.

With labeling changes, providing explanations and rationales for proposed labeling changes is a good practice for applicants and for FDA review teams.

This practice has helped both parties understand each other's reasoning, enabling them to respond effectively which then reduces the amount of back and forth required and the time required to complete negotiations on labeling.

The recommendation here is to include explanations or rationale for proposed label changes, either in written form or more informally as a good practice, to help each side understand what the basis for that is so that they can then respond effectively

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to what the thinking was.

In terms of inspection information, there's been inconsistent availability or communication of information about the status and results of inspections, hindering review transparency and predictability, both internally within FDA and between FDA and applicants.

Again, I can refer back to my earlier discussion in terms of to what extent the changes in management of inspections is, changing that, the insufficient data to make any firm conclusions about that.

Another note that I'd like to make is that in some cases, there are legal constraints around communicating the status of results of inspections with applicants.

For NDAs, a lot of times, applicants are using contact organizations, and there are legal issues around disclosing the results to the applicant as opposed to the site. With BLAs, more of those facilities are applicant-owned, and so that tends to come up less.

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The recommendation is to examine inspection information flows and communication channels with the aim of identifying improvements, and FDA is conducting such an examination.

All right. That's it. Thank you.

FDA Perspective

MS. HAFIZ: Thank you, Valerie. Now, we'll move into our panel session. The first panel will be made up of FDA staff and will focus on providing FDA's experience and perspectives on the program. If we can have our FDA panelists come up to the table.

Once all the FDA panelists have provided their perspectives, we'll ask that they take a seat in the front row so our industry stakeholders can come up.

FDA panelists, if you could introduce yourselves before you begin.

MR. FREY: Good morning. I'm Patrick Frey, chief of staff in the Office of New Drugs. I'll start off with comments on the FDA side.

Just to provide a little bit of a historical context first, the NME review program renegotiated this 2010, starting in 2010, and that wasn't (ph) coming off

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of the first two years of PDUFA IV, 2008 and 2009.

At that time, the new drug review process was really challenged mainly because of the new complex authorities we got at FDA (inaudible) that we had to implement, figure out, in a very short span of time, and then get used to them as well.

That was the context of our discussions for PDUFA V that led to the NME review program. I think at that time, there was a shared belief that by establishing communication points during the review process and lengthening the review time for FDA for (inaudible) applications, any NDAs or original BLAs that we might see an increase in the efficiency of the (inaudible) cycle.

No one was really certain at that time that it would do the trick. We spoke of the program in terms of it being a pilot actually. The minutes reflect this.

For a number of weeks during those PDUFA V discussions, we were talking about this being a pilot program. There was even discussion at the time that maybe we would look at an interim assessment of the

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program during PDUFA V and then figure out, do we want to discontinue it or not?

Those discussions continued, but then there was a sense that if we kept calling it a pilot program, maybe "pilot" would be thought synonymously in terms of it being temporary, and there would be a lack of commitment to it.

We dropped the "pilot" term at the time and recognized then that both FDA and industry were committed to the program and that it would be assessed twice during PDUFA V. Then we would figure out during PDUFA VI discussions what we wanted to do with the program.

I think the outcome that we've seen so far of the NME program, and the interim assessment, and in the final assessment has pretty much been a good report card for both the FDA and for industry.

Notably, during the interim assessment, it was just that the data was only enough at the interim assessment to show that we had a statistically significantly higher first-cycle approval rate for priority applications.

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Then for the final assessment, we've had enough experience with standard applications to say that, hey, across this program, when we compare it to the baseline, we have a better run (ph) and a more efficient first-cycle review process.

I think the NME program in PDUFA V formalized some practices that existed in some parts of our new drug review program and served to then make that a fully implemented component of new drug review. This is kind of baked into our review process now.

I think that the PDUFA VI agreement that published last summer proposes just some tweaks at the edges, that the program is viewed as a success. That's how the discussions were characterized during PDUFA VI, and we made some small changes to make it a little bit more flexible.

If a review team and the applicant have a different way that they like to do business during the review of a marketing application, they can do that as long as they reach agreement on how they're going to interact and communicate during the review of that application.

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I think from my own perspective, the PDUFA program has essentially spent 25 years now developing, refining, continuously improving a review process such that now, we're making marginal changes here and there which we did in PDUFA VI. I think we'll continue doing that going forward. Major changes to the review process just didn't happen in PDUFA VI.

When we talk about getting drugs to patients faster, I think now, the move is more to look at the full development timeline. Some of that was introduced in PDUFA V when we saw initiatives related to rare diseases, and biomarkers, and pharmacogenomics. Most of those were expanded then in PDUFA VI.

I think while the practices and principles of continuous improvement dictate that we continue to look at the review process to make sure it is run as efficiently as possible, now, I think there seems to be general agreement within the community that we operate in that getting drugs to patients faster now is about looking at the full development timeline and focusing energies there.

I want to thank ERG. They've been with us

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since 2012, summer of 2012, doing a very good job. Implementing the evaluation of the program as it was envisioned during PDUFA V discussions. During those discussions, we talked to industry about the fact that we felt we would need the contractors to basically be living with us. That's exactly what happened, being in person, attending all these meetings, witnessing the interactions so that we could get the best evaluation, the best feedback about the program.

I think we all recognized even during PDUFA V discussions, that was really going to be qualitative feedback that came from FDA review teams and from applicants in terms of how the interactions went.

Do you feel like the time spent with FDA during the review process was a good use of time? I think that the evaluation results speak pretty well to that.

I'll stop there and turn it over to my colleagues.

DR. UNGER: I'm Ellis Unger. I'm director of Office of Drug Evaluation I in the Office of New Drugs. I'm a signatory authority in the Office of Drug

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Evaluation I who oversees the divisions of cardiovascular and renal products, psychiatry, and neurology.

I take it you want my reflections now. My perception of the program is positive. I wouldn't even say generally positive. It's positive. I don't have any reservations about the program.

I think it's been a success. I think that giving extra transparency to industry is a good idea. In contradistinction to last-minute surprises that can't be remediated within the timeframe of a goal date, that was not a good idea, and this is definitely better.

I have one area I'd like to comment on specifically. I know the program pretty well because one of the problems I had was I had to provide a presentation of the program to all three of my divisions. I had to write a talk and do three one-hour talks to my three divisions explaining the program.

One of the things that was in the program that we haven't discussed this morning was the completeness of applications at the time of submission.

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One of the things that we were supposed to have obtained in the program was that all submissions were supposed to be complete. We were to threaten applicants that if they're submission was not complete that we could refuse to file it, and we would.

We didn't talk about this, and you don't (ph) show a slide on refused -- I don't think that there were a larger number of refused-to-file applications.

There was -- I will call it a drift in the three divisions that I oversee in that at the beginning, we tried to be dogmatic about this. We told the company, yes, you have to be complete or we won't file your application.

Basically, all three of the divisions' directors in ODE I wanted to be flexible, and so they all said, well, look, that's ridiculous. If they need to submit something in two or three weeks, that's okay.

That's what, in fact, happened. I think the program was a success, but I think there may be a disconnect now between what's actually written in the program which is no flexibility to be extended here versus what we did in practice.

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Patrick, you're probably the expert on what's in the program. I don't think the program was changed. I mean I never got a memo saying, we can be more flexible now. I think there could be a disconnect that maybe we should try to fix.

I think flexibility is a good idea. I don't think that part of the program was needed, that this draconian, you better submit something that's complete or we refuse to file.

Maybe you want to say something?

MR. FREY: We did institute a bit of flexibility for PDUFA V to allow for late submission, "late" defined as during the first 30 days after original receipt of the application, late submission of minor components of the application.

There are a small number of examples of what is a minor component of an application in the commitment letter. One thing that we didn't want to see was that at month 3, 4, or 5 that a whole new study comes in that we have to evaluate.

That was the extent of the flexibility that we established in the program, and that does not change in

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PDUFA VI.

DR. UNGER: In terms of some of the other things that seemed to be on the table right now, one is keeping track of the information requests, which seems to be a reasonable idea.

Although, as Valerie said, our concept of a complete response to an information request could be different from a company's. Answering the question versus making reviewers happy can be two different things. It's something, I think, that might be worth trying to put some effort into down the line.

In terms of labeling negotiations, I think there is some variation from division to division, and there probably some from office to office in terms of the actual nitty gritty negotiations that take place.

I know most of my divisions put -- we work within Microsoft Office Word, and we have track changes, and we also have balloons where we say, Dear Applicant, we changed this for such and such a reason.

I don't know if the industry is looking for a more explicit explanation or some other vehicle for explanation, but we do try to put in a label that, we

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took out this header because for whatever reason. Maybe other people could comment on that.

In summary, I'll say what I already said which is I think that the program has been a success. I don't have any reservations about it. It does require more effort on the part of our reviewers.

If we save ourselves a second cycle or a third cycle, that's huge savings right there. I think we all appreciate that this has been a positive change.

I'll stop.

DR. SMITH: My name is Jim Smith. I'm the deputy division director for the Division of Metabolism and Endocrinology Products in OND in CDER.

I would also echo that I think in general, the program has been very positive. I think that obviously, communication and transparency are the key objectives. I think that we were a division that was not -- as a general practice, our division did not hesitate to communicate even before the program with applicants regularly throughout a review cycle.

I don't know that there was a major shift in culture or practice. Formalizing the communication

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with respect to the mid-cycle and late-cycle communications, I think, does reduce some heterogeneity among different practices even within the division.

I think what it also does is by having formal touchpoints with the applicant, we have found it particularly useful in complex applications where there may be a multitude of consultants perhaps across centers.

Having some of those consultants at the table at a mid-cycle communication or a late-cycle communication, I believe, instills an extra sense of ownership to the review, to the consultants as well and really integrates them into the primary team.

We have certainly had -- I mean I'm speaking anecdotally. We've certainly had examples of reviews where early involvement from colleagues in CDRH with device-related issues, especially for combination products, and the fact that we will get their advice early before the mid-cycle has been helpful and has definitely led to first-cycle approvals.

Talking to Ellis' flexibility, we've had devices that were substantially altered during the

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review cycle but were still able to be reviewed in time enough so that they could be approved. Definitely, that has helped.

Regardless of the complexity of the application, it helps reviewers prioritize their reviews because they don't want to have a conversation with an applicant at the mid-cycle, having not hit the major potential showstoppers, if you will, and then have to surprise the applicant later in the review cycle. I think it does help to that regard.

We've had some experience with other pre-submission activities that under PDUFA VI would be optional; that is, on several occasions, we have granted and have given written responses for Type C meetings for just data structure, application structures, so not a data-driven meeting.

We've recognized that applicants can spend a fair amount of time programming from the technical aspects long before a pre-NDA or a pre-BLA meeting. If we have those interactions early, then we're more likely to get a package that we like to review at the pre-NDA and pre-BLA. We've found that to be helpful.

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With regard to the pre-submission meetings and the classical pre-NDA and pre-BLA meetings, I think that all of the enhanced communication and transparency that I believe has filtered down into the primary review staff and is becoming part of the culture is making folks take an increased ownership at those early pre-submission stages about designing the application that they would like to review instead of only reacting to the application that comes in the door.

That's challenging when -- obviously, industry has to do it all the time and take their best guess about what we want to see. It turns the tables a little bit by having our reviewers take some ownership in the application that they'd like to see, but all in all, I think that's a good thing.

We found the late-cycle meetings be a little bit less helpful. Obviously, if there were late showstoppers, I think that that could be a very useful meeting.

Applications that are destined for an advisory committee, I think the hope was the late-cycle meeting to kind of help coordinate that. In reality, the late-cycle meeting is so close to advisory committee meetings that if it's all timed properly that pretty much every has their meeting ready to go so that's it's a little bit late to get involved in that.

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But as I said, it isn't resource-neutral. I think that these meetings can be difficult. Even on our project managers, they can be very difficult to schedule, depending on the number of folks involved in the signatory schedule and the number of bodies that have to be in a room.

I think early on in PDUFA V, we made these meetings more laborious than they needed to be. Since, we've learned to stream line.

I think I'll go ahead and stop there. In summary, I think that hopefully -- and it sounds like, based on the final assessment, I think that there is some agreement on both sides that communication and transparency has increased. Certainly, I think that that's what we felt at the division level as well.

DR. JONECKIS: I'm Chris Joneckis. I'm the associate director for review management, Center for Biologics. I'm responsible for implementing all the user fees in the center.

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The program assessment that you saw was a combined CDER/CBER data. If you look at the CBER numbers, they pretty much overall have the same outcomes and observations that Valerie presented.

We have increased per cycle rates and decreased time to approval for priority over standard, in both categories as well. I think most of the patterns and attributes and things generally hold.

We have some smaller numbers, so it may be a little bit harder to make some of those observations. In general, we've seen those that that's pretty much the case.

The impact of the program, I'd like to say that it's built on longstanding traditions of what we've done at CBER and tried to have intensive communications, a lot of work during development. We have a lot of work from products for years and still do.

I think in the case that when the program came along, for folks who are doing all that, that was great. Perhaps for some that weren't, this made it

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even better.

It took a lot of the best practices that I think existed across the centers and made that a little bit more formalized, a little more process oriented and such in CBER.

I'll give you an example. We took the mid-cycle communications. We've always had mid-cycle internal meetings for years now. What we did is we said, okay, we're going to have a reviewer's report.

We had all the reviewers complete a very short targeted-focus reviewer report: what's the status of our reviews, what's the status of the information request from the industry, do I have hold issues, do I have issues that can't be resolved in the first-cycle?

We did that, and at first, a lot of people complained about it. We kept it short, very focused, and it actually facilitated over all the internal mid-cycle meeting. It made it a very more productive, efficient type of meeting where things could get discussed and get resolved in, say, an hour or an hour and a half and making any kind of course corrections that we needed.

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Again, I think the impact of the program was to formalize a lot of the good practices and principles that we've had. Overall, I think the reviewers like it.

RPMs love it. They like that structure. They like the focus. Anything that helps them manage, they like a lot. They weren't all converts in the beginning, but over time, I think that's where they are.

A couple of comments on inspection, inspections for biologics represents some unique challenges as Valerie, I think, had tried to indicate.

One example is just for the manufacturer of the drug substance or the active pharmaceutical. The facility typically has to be a manufacturer. Say, if you're manufacturing that product or a similar product, that, off the bat, changes when you're going to be able to have that inspection.

That requires a lot of pre-discussion with the company well before -- sometimes even before the pre-BLA meeting to schedule that. That's going to start to change the data that you see.

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The approach we take at CBER is sort of a continual assessment. We make assessments at the beginning just to determine what inspections have to be scheduled or not.

After our inspection, we work through our EIRs, our establishment inspection reports, issues that may come up on the 483s and such to try to resolve those.

We don't make a final determination on any of our facilities until the last 30 days before approval because it's not just the site we're looking at; it's the overall compliance history of that site, and other things may arise that can affect that.

To say that we make the determination in the last 30 days is also going to skew the data. We really don't have a site determination equivalent that, I think, CDER has evolved to over this process. Again, it's a little bit different.

We do work very extensively with manufacturers to try to resolves those issues that are outstanding to get them to an approvable facility, especially in the case of public health needs, breakthrough therapy

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products, shortage products, and thing of that nature. That can be literally working to the last day or so before approval with some of these companies.

The only other thing I guess I'd like to mention, as I think Ellis and others may have said, it's a two way street. Enhanced communication, enhanced transparency, predictability is all important.

I've been at CBER way too long now. We used to like to say, no surprises, and I actually heard Ellis said that. I don't think we see as many surprises as much anymore.

I think that's sort of evolved. I think the programs helped to get rid of those things. When we do see surprises, it's often from a more naïve company maybe that's not as familiar with the process and talking things through.

It is important that you have good quality applications, and that really does make it a lot easier. That can be everything from the discussion of the format, are you using the appropriate electronic format, are you using appropriate data standards formats to a lot of things. That really facilitates

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the review process.
That's pretty much it. I think moving into PDUFA VI, like Patrick said, there are minor tweaks and things. It gives a lot of additional flexibility for the agency and the applicant to determine what flavor really suits their purpose. I think that's actually a good thing.
We found in PDUFA V that the late-cycle meetings really weren't productive in a lot of cases, and we didn't need them. We never denied them. If the company wanted to have them; we had them.
As it evolved, we just said, there's no reason to have a late-cycle meeting. If it can be agreed by mutual agreement not to have them, we didn't.
Sometimes we turned those into labeling meetings; sometimes we couldn't because we still weren't there yet with the labeling. Again, we didn't have any real show-stopping issues.
Again, I think building in that flexibility will give us even additional benefits. Thanks.
MR. ISER: Good morning. I'm Bob Iser. I'm the director of the Office of Process and Facilities in

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OPQ within CDER.
A couple of things I wanted to react on. I'll focus most of my topics on inspections when it comes to CDER and then some of the things that we may be doing to address some of the observations that were made as this report was put together.
I'm also encouraged by the recommendations, the observations that were made. I think that it shows a lot of areas where we could still improve, and I think we are starting to improve within our office, and throughout CDER, and throughout the FDA.
I wanted to touch upon a couple of things that were noted in the presentation. The Office of Pharmaceutical Quality and the office I'm in stood up in January of 2015. At that time, we shifted the management of pre-approval inspections from the Office of Compliance to my office, the Office of Process and Facilities.
With that came some transition period. Luckily, the people that came into that office were people who were doing that work within the Office of Compliance for the most part. That helped in the

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transition.
Also, we saw that there were areas where we could be more communicative, more transparent internally and externally. We've been working over the past several years along with our colleagues in RA and then throughout CDER, again, as part of the whole program alignment activities that -- you know, where can we make our process more effective, more efficient, where can we communicate better, what are the clear roles and responsibilities in managing pre-approval inspections, and having really good discussions throughout CDER and RA, coming together with an agreed-upon concept that we can then operationalize which I think is very promising.
One of the other things we did was we said, well, let's separate out surveillance, or the general GMP inspections, from pre-approval inspections. That happened soon after the standup of OPQ.
Some of the data that you're looking at is a surveillance inspection maybe not triggered by the application but triggered on time since last inspection. There are different reasons why we might

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go out and inspect.
One of the reasons to separate also was the fact that time since last inspection as a standalone trigger is not appropriate risk-based decision to trigger a pre-approval inspection for an application coming in.
The surveillance inspection, while still informative to the approvability or non-approvability of an application, if there's a surveillance inspection happening, that doesn't mean we have to hold up an action on an application.
I think that's important, and that'll be something that I think we'll all see the impact of that a lot more of as we gather more data and as we have that process in place.
I wanted to also highlight a couple of things that they came up in the recommendations. This should not be any surprise as I bring these up.
A look in (ph) sponsors or the facilities that are communicating with us do, from a sponsor perspective, obviously, complete, accurate information coming in in the submission. It was highlighted about

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complete submissions.

Also, if there's any opportunities to do that before the NDA comes in, especially for these priority applications, have that information that's complete and accurate because it really, really impacts us if we're doing a more in-depth review or if we're doing an inspection and find another facility that was not listed in the application. Then we'd have to make a decision then and there, do we go and inspect that facility depending on the impact on the quality of that product.

Responsiveness of the facilities as we're going through and doing an inspection and then following up on that inspection, making sure that we get good responses from the facilities that it's done in those very tight timeframe so that we can make that final assessment decision.

And understanding, as I mentioned, that if things happen during the review cycle or during the inspection itself or we're seeing additional facilities, understand from the sponsor's perspective that that will impact the final assessment that we're

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doing, that overall facility assessment that was noted.

I'll wrap up with saying that -- well, I think it goes without saying that we're committed in FDA to be as transparent as we can. There are some limitations when it comes to the facility information, but I think we all benefit from being transparent and openly communicate where we can about the facility status, the inspection status, and that there will be times where we make a decision based on the fact that this facility may or may not be compliant or may be doing towards compliance, but we would hold up an action until we can get resolutions so that we can get that approval to benefit the American public as opposed to just reacting by sending a complete response, that that depends on responsiveness and also what we found in those facilities.

Thanks again for giving me an opportunity to react.

Industry Perspective

MS. HAFIZ: Thank you. If can have our FDA panelists move to the front row the industry panelists can come up.

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Thank you. Now, we're ready to begin our next panel session, focused on industry's perspectives and experience with the NME program.

Panelists, if I could just ask you to introduce yourselves before you begin speaking. Thank you.

DR. VERESHCHAGINA: Good morning, everybody. Lucy Vereshchagina. I'm vice-president of Science and Regulatory Advocacy for Pharmaceutical Research and Manufacturers of America, PhRMA for short.

As I mentioned, I'm speaking on behalf of PhRMA this morning. PhRMA represents the country's leading innovative biopharmaceutical research and biotechnology companies which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives.

PhRMA member companies are leading the way in search of new cures, investing in estimated $58.8 billion in 2015 alone in the discovery and development of new medicines.

On behalf of PhRMA, thank you for the

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opportunity to provide comments on the independent final assessment of the review program for NME NDAs and original BLAs.

Over the course of PDUFA V, the program has been successfully implemented by the agency as intended and outlined in the PDUFA V performance goals letter.

The program has achieved its goal of improving the effectiveness of the first-cycle review process to NDAs and BLAs. First-cycle approval rates reported in the final assessment report for the program are higher than they reported in the interim assessment with the overall first-cycle approval rates at almost 80 percent.

Overall, FDA sustained progress in the NME review process during PDUFA V, including the time for review and especially in the first-cycle approval rates which, in 2015, increased to 95 percent.

The final assessment determined that the differences in the first-cycle approval rates between the baseline and the program are statistically significant for both priority and standard applications.

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PhRMA supported the establishment of the program in PDUFA V and will look forward to working with the agency as the program continues in PDUFA VI.

PDUFA VI enhances the agency's ability to review innovative treatments and preserve the current eight months for a priority and 12 months for a standard review timelines for NDAs and BLAs.

As a result, patients in the United States will continue to benefit from timely access to safe and effective new medicines.

I'd like to make just a few brief comments on a few key issues in the final assessments. With regard to the program resources, similar to interim assessment, final reports states that the program has not been resource-neutral and has increased the burden on FDA primary reviewers and regulatory project managers.

The final review also states the review teams have been able to adapt to the new program milestones and goals and does acknowledge the dedication of FDA review staff to meet the goals despite the hiring challenges that the agency faced in the recent years.

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PDUFA VI helps to ensure that the FDA's resource and staff to support the regulatory review and approval process for new medicines, that they're scientifically sound, and efficient, and predictable.

With regard to PDUFA goal extensions and major amendments that were mentioned this morning, according to final report, almost 23 percent of applications in the program received a goal extension of three months due to major amendment.

Considering that the program application must be completed at the time of submission as agreed to by sponsor and FDA, and the increased program communication are intended to identify and resolve issues early in the review process, we would like to better understand the agency's rationale for (inaudible) *1:29:13 responses to information request as major adjustments and the timing of information requests that result in major amendments.

We recommend that the FDA explore ways to enhance the consistency across review divisions with regard to major amendments, particularly as it relates to decreasing the frequency of goal date extensions due

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to submission of relatively small amount of information in response to an information request.

With regard to inspections, we agree that the final assessment finding that inconsistent availability and communication of information about the status and results of inspection has hindered review timeline transparency and predictability.

The final report states that only 46 percent of program applications received inspection that were completed within program timelines. For those that were not completed within the program timelines, the majority were due to the late completion of GMP inspections.

PhRMA is pleased that the agency is undertaking review of inspection information flow, considering that the final report states that the applications receiving on time inspection received first-cycle approval over one and a half months earlier than those applications that did not receive on time inspections.

With regard to review communications, the success of the program relies on effective two way

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communications between FDA and the sponsor throughout the drug development and regulatory review process.

We definitely appreciate FDA's effort to be responsive to feedback emerging from early experience with the program and the agency's implementation of better practices in real time.

We're pleased to see that the final report states that the agency addressed mid-cycle communication and signatory authority issues raised in the interim assessment by implementing refined guidelines.

We encourage the FDA to continue promoting policies and procedures that ensure that robust engagement occurs consistently at both mid-cycle and the late-cycle meetings.

In conclusion, we appreciate the agency's effort to meet the program's goal as outlined in PDUFA V and would like to thank FDA for bringing all stakeholders today an efficient and effective review process critical for ensuring timely patient access to innovative safe and effective new drugs and biologics.

We look forward to working with FDA and all

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stakeholders as the program continues in PDUFA VI. Thank you.

DR. METCALF: Good morning. My name Rob Metcalf, and I'm the vice-president of Diabetes Clinical Development and Clinical Transformation at Eli Lilly and Company.

I'm also the past vice-president of Global Regulatory Affairs, and in that role, did have the opportunity to oversee submission applications to the FDA under the program.

Thank you very much, on behalf of Eli Lilly, to be here to comment today on the program. Thank you to the Eastern Research Group and Valerie for the excellent presentation that you did today.

I think that just reemphasizes the overall success of the program. Increasing our first approval rates to 80 percent over the baseline certainly exemplifies the overall goals of continuing to ensure timely delivery of safe, effective, and high quality new medicines to patients in need.

Certainly, this has been Lilly's experience as well. Overall, we view the program as being very

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successful in helping to meet those goals and objectives.

I was honored to be a member of the PDUFA VI negotiating team that negotiated the commitment letter that hopefully will become effective by the end of Q3 this year.

In that letter, we institutionalized many components of the program, and that demonstrated our company's support for the excellent elements that we saw in PDUFA V, moving them into and making them permanent as part of PDUFA VI.

As I've said, our overall Lilly experience with the program has been very positive. We've seen significantly improved two-way communication with review staff as compared to our PDUFA IV experiences.

In particular, the mid cycle meetings and late-cycle meetings have facilitated a higher level of review transparency as compared to previous programs.

Furthermore, we've seen a much higher level of openness by review staff to ad-hoc communications, either through teleconferences, rapid email exchanges and occasional face-to-face meetings that have

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facilitated the review process, have been beneficial in aligning the FDA and the sponsor, Lilly, to lead to quicker resolution of issues.

Lilly views communications during the pre-submission meetings as critically important to overall review success. The communications allow for better planning of application content to ensure a complete application, but more importantly, help us to work with the FDA on the nuances of applications. As Jim pointed out, some of those, at times, can be challenging to work through.

We have found that having more than one meeting with the FDA in advance of an application is beneficial, and that's been pointed out in the Eastern Research Group comments and feedback that you've received.

We'd encourage the FDA to continue to use this paradigm when working with sponsors on applications, particularly those applications that may be more complex in nature. As Valerie pointed out, there may be different paradigms to do that, but we've seen that as valuable as a sponsor.

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Lilly has derived notable value in meetings with the FDA team during both the mid-cycle and late-cycle review meetings. The holistic multidisciplinary discussion of application status during those meetings gives insight into the timeline for FDA's review and action and helps focus attention of the key players on resolving review issues and concerns.

This increased level of transparency is critical to a company as we prepare for potential approvals and potential launches.

Identifying and raising review issues and concerns at these meetings and avoiding new issues coming up late in the review process, particularly after the late-cycle meeting, is key to review success.

Substantive review issues or significant labeling challenges brought up late in the review cycle, close to the action dates tend to defeat the purpose of the mid-cycle and late-cycle meetings and do make it challenging for both sponsors and the FDA to ensure effective and efficient reviews. From our experience, this should be an area of ongoing focus for

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both sponsors and the agency.
As I stated previously, the proposed PDUFA VI commitment letter builds upon the successes of the program and makes permanent the key components of the program, allowing sponsors and the FDA to benefit from the process improvements indefinitely.
The goal of the program continues to be to promote the safe and effective development of new medicines and delivery of those in a timely manner to patients in need.
FDA has been asked under PDUFA VI to update the Good Review Management practices guidances, and this is an opportunity for FDA to address other noted and important areas of review such as enhanced communications regarding the type and rationale for post-marketing commitments and post-marketing requirements.
In conclusion, I would like to thank the agency for your efforts to meet the program's goals as outlined in PDUFA V. I believe the agency has not only met those goals but in many ways have exceeded those goals. We look forward to continuing elements of the

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program under PDUFA VI. Thank you.
DR. KHAN: Hello. I'm Tahira Khan, an associate program director at Genentech. I'm also in regulatory affairs. I also work in the policy office here in Washington, DC.
I'd like to thank you for having me here and share Genentech's experiences with the PDUFA V program.
Overall, our experience with the program has been very positive. The program clearly improved review efficiencies and has helped create greater transparency and open communication between industry and the FDA.
We had a number of breakthrough therapy designated products that went through review cycle under this program. This review pathway has also worked really well for Genentech.
FDA was readily available to talk to the product teams and shared their evolving thinking around complex issues throughout the review which was very well-appreciated by the teams.
The additional face-to-face meetings under the breakthrough therapy review pathway helped later

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interactions with the agencies via phone and other means.
For example, for one particular breakthrough therapy designated product, we had multiple collaborative meetings with the FDA that helped us to incorporate FDA's request in the dossier and resulted in rapid BLA review timelines and early approval.
Having combined BLAs with two different indications under one review division was also very efficient. FDA worked with us to accept late data in an efficient manner, focusing on what was important in the process.
In terms of best practices and learnings, I could share that maintaining early and open channels of communication is critical to the success of the review process.
Insight into FDA's thinking on evolving strategy and review can really help industry understand information request from the FDA upfront rather than by follow-up conversations.
Starting an early dialogue with both review divisions and CDRH for products with the diagnostic is

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also very important.
Proactively providing the FDA methodology for analyses conducted and new label information was also essential, and it helped decrease the back and forth communication.
From our end, frontloading of task such as labeled text (ph) was very helpful with the speed of the review.
For breakthrough therapy designated products, requests for information can be issued very quickly after submission of NDA, and it is very important for the sponsor to develop a process for responding to these requests early and align with filing team members.
It is also important to ensure that all manufacturing sites are listed by the industry as inclusion of new manufacturing sites could prompt inspection which could prolong assessment.
We do recognize that it is also essential for quality requirements to keep base with clinical and nonclinical development programs for fast track products to shorten timeline to approval.

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Label negotiations can go very fast with multiple interactions even in one day. Therefore, it is essential to have clear processes and structure in place.

In terms of improvements, the evolving landscape and thinking did lead to some inefficiencies and unpredictability which however we think is understandable.

It would be helpful for the sponsor to know certain submission requirements ahead of time, such as request for financial disclosure forms and summaries. Information requests from the agencies are sometimes difficult to provide and can take time on the sponsor side.

Once responses are submitted, it would be good to get some follow-up feedback from the agency on the responses submitted and whether they were informative or not. In certain instances, it may also be helpful if we had requested teleconferences to clarify certain FDA information requests.

The agency requested certain safety analyses based on data points that were not prospectively

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collected in the studies, and this was for certain products, but they did not provide detailed guidance on methodology.

Although we had provided our methodology in the pre-BLA pre-meeting package, but we did not receive feedback. So it would be helpful for us to get this feedback early.

During the last stage of the review, it would also be helpful if the agency could provide information on what their target date is for signing the approval letter.

Overall, we've been very pleased with the efficiencies that we observed at the review timelines and processes. We hope to continue to build on our interaction and communications with the agency.

We thank the agency for it.

MS. HAFIZ: Thank you. If you want, you can just stay there. That's fine.

We're now moving into our open public comment session. I'm going to check with my colleague, Yoni (ph), to see -- okay. It looks like we don't have anyone who signed up for the open public comment

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session.

Do we have any other questions?

(No response.)

No. Okay. So we are really ahead of schedule. That concludes this meeting. Thank you to everyone who came out today.

As a reminder, the public docket is open until next Monday, April 3rd. You can submit any comments over there.

If you are a non-FDA attendee, I'm just going to ask if you can stay behind so we can escort you out of this building. Thank you very much.

(Whereupon, at 12:45 p.m., the meeting was adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

MICHAEL FARKAS

Notary Public in and for the

District of Columbia

CERTIFICATE OF TRANSCRIBER

I, CINDY MCALLISTER, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

April 6, 2017

DATE CINDY MCALLISTER

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