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FINAL ASSESSMENT OF THE PROGRAM
FOR ENHANCED REVIEW TRANSPARENCY
AND COMMUNICATION IN PDUFA V

Monday, March 27, 2017

Location:

Food and Drug Administration (FDA)
10903 New Hampshire Avenue
Silver Spring, MD 20903
5635 Fishers Lane

Reported by: Michael Farkas,

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<p style="text-align: right;">Page 6</p> <p>1 2 Tahira Khan 3 Genentech 4 Associate Program Director, Clinical 5 Regulatory Affairs 6 7 Q&A and Public Comments 8 - No questions or discussion 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>	<p style="text-align: right;">Page 8</p> <p>1 We will then have panels composed of FDA staff 2 and industry stakeholders who will provide their 3 experience and perspectives on the program. We will 4 start with FDA panelists and then transition to the 5 industry stakeholder panelists. 6 After the panelists, we'll have time for 7 public comments, and you can sign up at the 8 registration table right outside if you would like to 9 provide a public comment. 10 Before I hand it over to Valerie, just a 11 reminder that the restrooms are located in the hallway 12 on the right side of this room. Now, I'll turn it over 13 to Valerie. Thank you. 14 Presentation of the Final Assessment 15 MS. OVERTON: All right. Thank you very much. 16 As Azada said, my name is Valerie Overton. I'm with 17 Eastern Research Group, the independent contractor who 18 conducted the evaluation of the FDA's program for NME 19 NDAs and the PDUFA V. 20 What I'll be doing first is to just provide a 21 little bit of background and introduction and then go 22 over some highlights of our results of the evaluation,</p>
<p style="text-align: right;">Page 7</p> <p>1 PROCEEDINGS 2 (11:01 a.m.) 3 Welcome 4 MS. HAFIZ: Hello, and good morning. Welcome 5 to the public meeting on the final assessment of the 6 program for Enhanced Review in Transparency and 7 Communication in PDUFA V. 8 My name is Azada Hafiz, from the Office of 9 Strategic Programs in the Center for Drug Evaluation 10 and Research, and I will be your moderator today. 11 In today's meeting, the independent contractor 12 will discuss the findings of the final assessment, and 13 public stakeholders will have an opportunity to present 14 their views on the program. 15 I do want to mention that in addition to this 16 meeting, a docket will be open until next Monday, April 17 3rd, to which the public may submit comments regarding 18 their perspectives on the final assessment. 19 The agenda for today's meeting is Valerie 20 Overton, the vice-president of ERG Eastern Research 21 Group; the independent contractor who conducted the 22 program evaluation will present the final assessment.</p>	<p style="text-align: right;">Page 9</p> <p>1 answer the assessment questions, and talk about our 2 findings and recommendations. 3 To start, what we were charged with doing was 4 to look at every NME NDA and original BLA with the 5 first-cycle action in PDUFA V. The scope of the 6 program compasses all of that. We looked at every 7 application that went through the program, up through 8 our cut-off date for the evaluation. 9 The program includes some major attributes 10 such as mid-cycle communication, late-cycle meeting, a 11 review clock that begins on the 60-day filing date. 12 The goals of the programs were really to 13 improve communication between applicants and FDA review 14 teams, to improve the transparency of reviews, and to 15 improve the efficiency and effectiveness of reviews. 16 If all of those things happen, then one would 17 expect that there would be a smaller number of review 18 cycles to get to the point of approval for where that's 19 warranted based on the efficacy and safety of the 20 product being reviewed. 21 Our program evaluation was something that was 22 a commitment made for PDUFA V. We were charged with</p>

<p style="text-align: right;">Page 10</p> <p>1 identifying relationships between program attributes, 2 review process attributes, and application attributes, 3 and the first-cycle regulatory outcomes, and time to 4 first-cycle regulatory outcomes.</p> <p>5 We're looking at lots of different aspects of 6 applications in the review process and seeing what that 7 looks like in terms of first-cycle actions and the 8 timing of the review. We were also charged with 9 looking at how applicants and FDA staff characterize 10 communication and application reviews in the program.</p> <p>11 In order to accomplish this evaluation, we 12 began with a set of assessment questions having to do 13 with the goals we just described. We developed a set 14 of detailed metrics and protocols and instruments in 15 order to collect the data for those metrics.</p> <p>16 We collected the data by observing meetings 17 between FDA and applicants, by reviewing documentation, 18 and by interviewing both applicants and FDA review 19 teams separately after the first-cycle action has been 20 taken.</p> <p>21 We then looked at that data in terms of 22 descriptive, statistical, and qualitative analyses, and</p>	<p style="text-align: right;">Page 12</p> <p>1 When we look at what happened with all of 2 those applications, we looked at, of course, the first- 3 cycle approval rate, the number of complete responses, 4 the number of withdrawals after filing to get our total 5 numbers.</p> <p>6 What we saw in the program was a statistically 7 significantly higher first-cycle approval rate that was 8 79.5 percent on average over the course of the first 9 roughly four years of program compared to 54.8 percent 10 in PDUFA IV.</p> <p>11 We also looked at the milestone communications 12 I mentioned. The program instituted some requirements 13 for the pre-submission meetings, some recommendations 14 for the pre-submission meetings, and a mid-cycle 15 communication, and a late-cycle meeting.</p> <p>16 Given when they occur, the topics discussed 17 are probably not too surprising. In the pre-submission 18 meeting, the topics that are most frequently discussed 19 were product quality, topline results and data, and the 20 format and content of submission, what you would expect 21 in the meeting before submission.</p> <p>22 In the mid-cycle communication, the topics</p>
<p style="text-align: right;">Page 11</p> <p>1 developed a set of findings and recommendations.</p> <p>2 Our interim report was after the first two 3 years of the program, and that was published in March 4 2015. This final report was after roughly four years 5 of the program and was published December 31st, 2016. 6 That is the subject of this presentation.</p> <p>7 The final report is online, on FDA's website. 8 This is the table of contents, if you will, just a 9 summary of what's in that report.</p> <p>10 To start out with, in terms of the 11 applications that we were looking at, we were comparing 12 applications under PDUFA IV and PDUFA V for the program 13 for NME NDAs and original BLAs.</p> <p>14 All of the applications that we looked at were 15 ones that have been filed and received the first-cycle 16 action. In the program that totaled 171 applications; 17 in the baseline, there's 219 applications.</p> <p>18 Remember, there were more in the baseline 19 because we were looking at all of PDUFA IV as opposed 20 to just the first almost four years of the program. 21 There are a greater number of applications in the 22 baseline for that reason.</p>	<p style="text-align: right;">Page 13</p> <p>1 that were most frequently discussed were clinical, 2 product quality, and then a bunch of other topics 3 including labeling, PMR/PMC, a late-cycle meeting, 4 safety, pediatrics, REMS, and so forth.</p> <p>5 In the late-cycle meeting, the topics that 6 were most frequently discussed were review issues, and 7 labeling, and PMRs and PMCs. Those really reflect what 8 you would expect based on the timing of those meetings 9 throughout the review cycle.</p> <p>10 Based on our observations of these meetings 11 and also results from the interviews with both 12 applicants and FDA staff, we heard frequently that the 13 value of the communication was seen as quite high.</p> <p>14 The applications especially appreciated the 15 open and early communication from the pre-submission 16 meeting through the mid-cycle communication and the 17 ongoing open communication through the late-cycle 18 meeting.</p> <p>19 There was a lot of benefit perceived by the 20 applicants who we interviewed in terms of the 21 discussions of the understanding of what the 22 expectations were for submission in the pre-submission</p>

<p style="text-align: right;">Page 14</p> <p>1 meeting and the assessment of the readiness to submit 2 in the pre-submission meeting.</p> <p>3 Then in the milestone meetings, during the 4 review itself, again, the open communication and 5 especially developing that shared understanding of the 6 progress and potential issues so that the review 7 itself, and the progress, and the issues have a high 8 level of transparency associated with them. Because of 9 that, there was an opportunity to work and to 10 understand the issues and work to resolve them where 11 possible.</p> <p>12 As I mentioned, the first-cycle approval rate 13 was higher in the program than in the baseline. If you 14 look at all applications, only priority applications, 15 or only standard applications, in all three cases, the 16 first-cycle approval rate is higher in the program than 17 in the baseline. Those differences were statistically 18 significant.</p> <p>19 In terms of what applications were most likely 20 to receive first-cycle approvals, we found that those 21 aimed at unmet medical needs, tended to have higher 22 first-cycle approval rates than others.</p>	<p style="text-align: right;">Page 16</p> <p>1 expected, the median time to first-cycle action was 2 longer in the program than in the baseline. There is a 3 two-month difference because of the review period 4 starting 60 days from the receipt.</p> <p>5 Accordingly, in general, the time to 6 first-cycle action, whether it's approval or otherwise, 7 was roughly two months longer in the program than in 8 the baseline.</p> <p>9 Patterns, in terms of time to approval, so the 10 main patterns had to do with, on the one hand, 11 prioritization of the application. Applications that 12 had special designations such as priority review, a 13 breakthrough therapy designation, and so forth, those 14 kinds of prioritized applications tended to have a 15 shorter review than those applications that did not 16 have special designations.</p> <p>17 In terms of applications that had a longer 18 time to approval, again, as one would expect, they 19 would be applications that did have goal extensions 20 because that extends the review clock, a longer than 21 average primary review time, and one or more 22 deficiencies identified at the late-cycle meeting.</p>
<p style="text-align: right;">Page 15</p> <p>1 Those with priority review tended to have 2 higher approval rate. The other category that had a 3 higher approval rate were those with major amendments 4 and goal extensions.</p> <p>5 In the program, the expectation is that there 6 would be a goal extension when there was an opportunity 7 to -- hopefully, an opportunity to address and resolve 8 issues in time for a first-cycle approval with an 9 extended PDUFA goal date. Indeed, we did find that in 10 those situations, there was a higher approval rate.</p> <p>11 In terms of applications with lower approval 12 rates, these aren't really a surprise either when 13 there's a longer-than-average primary review time, one 14 or more significant issues identified at the mid-cycle 15 communication, and at the late-cycle meeting.</p> <p>16 All of those three characteristics have to do 17 with applications that just have more challenges. 18 There are more issues; they're more problematic, and so 19 those tended to have a longer primary review time as a 20 result and also, a lower approved first-cycle approval 21 rate.</p> <p>22 In terms of time to first-cycle action, as</p>	<p style="text-align: right;">Page 17</p> <p>1 Those are situations where the full review clock was 2 needed in order to look at the application.</p> <p>3 I mentioned special designations, and so I 4 just wanted to cover that a little bit more. There 5 were relatively high first-cycle approval rates and 6 relatively short time to approval for applications with 7 special designations.</p> <p>8 Here, you see various groups of program 9 applications with just a selected sampling of special 10 designations compared to all program applications as a 11 whole.</p> <p>12 You see that a higher proportion of those 13 applications with special designations had first-cycle 14 approval rate, had shorter time to first-cycle 15 approval, and of course, those are the ones that 16 generally received priority review as well.</p> <p>17 I also mentioned goal extensions. In the 18 program, as I mentioned, the expectation was that the 19 goal extensions would be issued primarily when there 20 was an opportunity to then resolve any remaining issues 21 and achieve a first-cycle approval where warranted, 22 where the application showed sufficient efficacy and</p>

<p style="text-align: right;">Page 18</p> <p>1 safety.</p> <p>2 With that as an expectation, we did indeed see</p> <p>3 that applications that received a goal extension were</p> <p>4 more likely to receive first-cycle approval, and that</p> <p>5 was certainly true in the program as compared to the</p> <p>6 baseline which is PDUFA IV.</p> <p>7 Similarly, the time after the original</p> <p>8 submission of the goal extension was issued was much</p> <p>9 more variable in the program than in the baseline</p> <p>10 because in the program, there was the opportunity to</p> <p>11 issue a goal extension really at any time during the</p> <p>12 review. You see a broader range of times for when the</p> <p>13 goal extension was issued in the program than it did in</p> <p>14 the baseline.</p> <p>15 All right. Inspections. So in the PDUFA V</p> <p>16 program guidelines, the expectation for applications in</p> <p>17 the program is for inspections to be completed within</p> <p>18 six months of receipt for priority applications and</p> <p>19 within ten months of receipt for standard applications.</p> <p>20 There are a lot of different ways to think</p> <p>21 about inspections. There is the actual conduct of the</p> <p>22 inspections themselves at the facility, there is the</p>	<p style="text-align: right;">Page 20</p> <p>1 sites come up that are found to need inspection that</p> <p>2 was not clearly laid out initially in the application.</p> <p>3 After that planning and preparation phase,</p> <p>4 there is the actual conduct of the inspections at the</p> <p>5 sites. Those usually take place between months four</p> <p>6 and eight and again, can extend later if more site</p> <p>7 inspections were needed either because new sites were</p> <p>8 found or because it turns out that a site needs to be</p> <p>9 re-inspected.</p> <p>10 Then the next things, and these are all</p> <p>11 overlapping phases as you can see because the</p> <p>12 variability in terms of the number and location of</p> <p>13 inspections, when it's determined that sites need to be</p> <p>14 inspected, whether the inspections aren't needed, and</p> <p>15 so forth.</p> <p>16 The next phase is the resolution of any issues</p> <p>17 that are identified during the inspection. That is</p> <p>18 extremely variable in duration depending on the number</p> <p>19 and severity of issues.</p> <p>20 The goal is to resolve all of those issues in</p> <p>21 order to achieve approvability. Of course, that</p> <p>22 doesn't always happen, but that is the goal of this</p>
<p style="text-align: right;">Page 19</p> <p>1 process of resolving issues that are identified, and</p> <p>2 then the final recommendation about the acceptability</p> <p>3 of the sites.</p> <p>4 For the purpose of this evaluation, inspection</p> <p>5 completion was defined as the last overall site</p> <p>6 acceptability recommendation for CDER and the latest</p> <p>7 GMP or GCP site inspection date for CBER. The reason</p> <p>8 why it's different between CDER and CBER is because the</p> <p>9 data that were available to us were different.</p> <p>10 I just want to illustrate what that means in</p> <p>11 terms of what we're looking at in terms of timing for</p> <p>12 when we define inspection completion this way. For the</p> <p>13 inspection process, first, of course, there is the</p> <p>14 planning preparation phase where FDA is looking at a</p> <p>15 site list submitted with the application, evaluating</p> <p>16 what sites need to be inspected, scheduling and</p> <p>17 coordinating involved in that kind of preparation that</p> <p>18 happens.</p> <p>19 That usually happens in the first few months</p> <p>20 after receipt and can extend later if more site</p> <p>21 inspections were needed because sometimes during the</p> <p>22 course of review, additional inspections, additional</p>	<p style="text-align: right;">Page 21</p> <p>1 phase of the inspections process.</p> <p>2 Then, there is the kind of final stage of the</p> <p>3 inspection process which is preparing the overall site</p> <p>4 recommendation and decision. Again, when that happens,</p> <p>5 it's extremely variable depending on all of the factors</p> <p>6 I mentioned with the number and location of the sites</p> <p>7 that need to be inspected, for example, whether if</p> <p>8 there's just one or two, whether they're in the United</p> <p>9 States versus in other countries, the number and</p> <p>10 severity of issues that are uncovered, whether</p> <p>11 additional sites need to be inspected, or whether a</p> <p>12 site needs to be re inspected, and so on, and so forth.</p> <p>13 That is an extremely variable period of time.</p> <p>14 In some cases, there's also multiple site</p> <p>15 recommendation dates because there is an initial site</p> <p>16 recommendation date, and then further activity happens,</p> <p>17 and then there is a second site recommendation.</p> <p>18 In this process, the last date here, the</p> <p>19 recommendation and decision date, is the one that we</p> <p>20 used for inspection completion in CDER. For CBER, it</p> <p>21 was the date of the last site inspection, so earlier in</p> <p>22 the process.</p>

<p style="text-align: right;">Page 22</p> <p>1 That is going to be important because what we 2 saw, of course, using these different definitions, is 3 that the CBER sites tended to be completed earlier than 4 the CDER sites because of that difference in 5 definition.</p> <p>6 Here, what I'm showing you is a distribution 7 of the inspection completion dates for the applications 8 in the program. This is just the site completion, that 9 earlier phase before all the resolution has happened 10 and before there's been a recommendation on the site.</p> <p>11 You can see that the bulk of the sites are 12 inspected between months four and eight, with some 13 occurring earlier or later, depending on review 14 priority or whether there were additional sites that 15 needed to be inspected, or whether there was a goal 16 extension, and so some of the inspections took place 17 later than was typical.</p> <p>18 Here, I've added on the recommendation date, 19 the last recommendation date. Here, you can see in the 20 blue, again, the site completion dates; and in the red, 21 you see the recommendation dates.</p> <p>22 Again, the inspections themselves typically</p>	<p style="text-align: right;">Page 24</p> <p>1 occurred kind of midway through the program. We would 2 expect that there would be some observations around 3 that in terms of what we saw with the inspections. 4 Whether that changed the results or not, that's just an 5 important change to note as context for our results.</p> <p>6 What we noted starting with the interim report 7 was that historically, it was challenging for FDA 8 reviewers and applicants to know the status of 9 inspections. That was one of the findings that we 10 found in the interim report.</p> <p>11 Given this transition that took place kind of 12 midway through the program, there was kind of the first 13 couple of years with the old management of the 14 inspection process and then a transition period where 15 applications were now the responsibilities for CDER and 16 the NDAs. It was consolidated under OPQ, and there was 17 some transition period for that. Then after that, 18 things settled in place in terms of OPQ overseeing the 19 inspections process.</p> <p>20 After the transition period, we haven't had a 21 long enough period of experience with those 22 applications that had inspections after the transition</p>
<p style="text-align: right;">Page 23</p> <p>1 took place between months four and eight. The 2 recommendations typically took place months five and 3 twelve, depending on the whole range of factors that I 4 mentioned.</p> <p>5 In terms of what we found, there's another 6 wrinkle that we wanted to mention in terms of providing 7 context for the inspection results. At the time of the 8 interim report, there had been one process and managing 9 structure in place for inspections.</p> <p>10 Just after the interim report was published, 11 FDA transitioned to a different structure for managing 12 the inspection process. Management of CDER's 13 pre-approval inspection process responsibilities were 14 consolidated under the Office of Pharmaceutical 15 Quality, OPQ.</p> <p>16 So is the case (ph) after that transition that 17 ORA leads and conducts most pre-approval inspections 18 performed for NME NDAs, but OPQ performed the initial 19 facility evaluation, participates in some pre-approval 20 inspections, and makes the final facility 21 recommendation.</p> <p>22 The reason why I bring this up is that this</p>	<p style="text-align: right;">Page 25</p> <p>1 period was complete in order to make any firm 2 conclusions about changes in transparency, 3 communication, and so on, and so forth as of the 4 cut-off for the final report, which was June 2016.</p> <p>5 The program evaluation completion target were 6 met for 46 percent of program applications. Again, 7 when I doggedly went through those slides about how we 8 are defining inspection completion for the purpose of 9 the program evaluation is for the bulk of applications 10 for CDER applications -- that last recommendation date. 11 That last recommendation date includes all of the time 12 that we spend resolving -- of course, after all the 13 time spend resolving issues.</p> <p>14 That last recommendation date, over 50 percent 15 of the time occurred after the target of six months or 16 ten months depending on the application receipt, 17 depending on whether it was standard or priority.</p> <p>18 There are a lot of reasons for that. The 19 reasons for the final recommendation happening later in 20 the process include situations where there were enough 21 issues that needed to be resolved, that they couldn't 22 be resolved by that six- or ten-month date, that there</p>

<p style="text-align: right;">Page 26</p> <p>1 was continuing efforts to resolve those issues after 2 that time so that there could get to a point of 3 approvability in time for first-cycle review. 4 In some cases, the reason for that was the 5 need for more inspections late in the process and as I 6 mentioned, attempt to achieve acceptability in time for 7 first-cycle approval. There are a whole bunch of 8 reasons why the completion target date was only met 9 roughly 50 percent of the time. 10 I could go on and on about this because it's 11 easy to look at that number and think, that looks 12 pretty bad. When you look at what's going on during 13 that time, what we heard, what we observed, what we 14 heard from FDA staff in interviews, what we heard from 15 applicant in interviews suggests that that is a very 16 productive time to resolve issues. 17 That late date is not necessarily a bad thing; 18 often, it's a good thing because if you had to do the 19 site recommendation by that six-month or ten-month, you 20 would more often have to recommend against approval 21 whereas continuing to work after that date, then they 22 (inaudible) to work to happen to resolve issues so that</p>	<p style="text-align: right;">Page 28</p> <p>1 time, there hasn't been a lot of time for applications 2 that receive a CR to resubmit and then have a 3 second-cycle action. The sample size is too small for 4 a statistical analysis at this time. 5 As of the cut-off analysis for the final 6 report, there had been 11 program applications 7 resubmitted, compared to 65 applications resubmitted 8 from the baseline, from PDUFA IV. Again, remembering 9 that the two reasons for that is one, there were 10 smaller proportion of applications that received a CR 11 to begin with and then not as much time has elapsed for 12 a significant number of resubmissions to take place; 13 whereas with PDUFA IV, there's been all of these years 14 since then for a resubmission to take place. Those are 15 highlights of the results. 16 Now, what I'm going to do is to look at the 17 evaluation questions or assessment questions that were 18 laid out for this evaluation. 19 The first pair of questions has to do with: 20 What is the relationship between program attributes and 21 first-cycle outcomes? What is the relationship between 22 program attributes and time to first-cycle outcome?</p>
<p style="text-align: right;">Page 27</p> <p>1 there could be approval. 2 Complete response letters, I mentioned that 3 the first-cycle approval rate is high in the program, 4 has been high in the program which means that the CR 5 rate is low. The number of CR letters is relatively 6 small compared to the baseline. 7 What we see here are what the top three issues 8 that are cited in complete response letters: efficacy, 9 product quality, and safety. For the most part, 10 there's not a big difference between the issues that 11 are cited in the program, the CR letters in the program 12 versus in the baseline. 13 The exception to that is that safety is more 14 often cited in CR letters in the program than in the 15 baseline than in the program. I would just caution, 16 again, that the numbers are small, and so I would be 17 hesitant to read too much into those numbers. They're 18 certainly not statistically significant, given the 19 small numbers. 20 Time to resubmission, once an application had 21 been CR'd, then there's the opportunity to resubmit. 22 Given that the program is still continuing through this</p>	<p style="text-align: right;">Page 29</p> <p>1 As I mentioned, that relationship between 2 program attributes and first-cycle regulatory outcomes, 3 for the program as a whole, is that the first-cycle 4 approval rate was statistically significant and higher 5 in the program than in the baseline. 6 For time to first-cycle outcome, the 7 first-cycle reviews took longer in the program than in 8 the baseline as expected. Nevertheless, in interviews 9 with applicants, they still -- despite that difference, 10 still view the program as having value in enhancing 11 review transparency, communication, predictability, and 12 efficiency. 13 In the interviews with applicants, there was 14 still a positive perception of the program regardless 15 of the time that it took to get to first-cycle outcome. 16 The second pair of questions has to do with: 17 What's the relationship between review process 18 attributes and first-cycle outcome, and time to first- 19 cycle outcome? 20 Review process attributes, we looked at the 21 priority of review, major amendments, and a whole bunch 22 of other metrics. These are examples of metrics that</p>

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<p>1 stood out.</p> <p>2 Two attributes were associated with higher</p> <p>3 first-cycle approval rates, priority review, and the</p> <p>4 goal extension as I mentioned. One attribute was</p> <p>5 associated with the lower first-cycle approval rate,</p> <p>6 that being a longer time to primary review completion.</p> <p>7 What I would just remind you of with that one</p> <p>8 is that the longer time to primary review completion</p> <p>9 tended to be associated with applications that had more</p> <p>10 issues. It's not that FDA was taking longer for the</p> <p>11 same quality application; it had to do with</p> <p>12 applications that had more -- so it's really a circuit</p> <p>13 for applications that had more issues.</p> <p>14 In terms of time to first-cycle outcome, the</p> <p>15 two attributes that were associated with longer meeting</p> <p>16 time to first-cycle approval was, again, the longer</p> <p>17 time to primary review completion and of course, having</p> <p>18 the goal extension which extends the review clock.</p> <p>19 The next pair of questions has to do with the</p> <p>20 relationship between application attributes, and first-</p> <p>21 cycle outcomes, and time to first-cycle outcome. What</p> <p>22 we saw with the applications is that applications that</p>	<p>1 resolving questions and issues. The review staff,</p> <p>2 similarly, described the communications under the</p> <p>3 program as constructive.</p> <p>4 One thing that I wanted to mention here in</p> <p>5 terms of the applicants' characterizations of the</p> <p>6 communication is many applicants went out of their way</p> <p>7 to describe the review staff, and especially the RPM,</p> <p>8 the regulatory project manager, as being very</p> <p>9 responsive, constructive, and flexible, and expressed a</p> <p>10 great deal of appreciation for the efforts of those FDA</p> <p>11 staff.</p> <p>12 There had been comments, again, on an ongoing</p> <p>13 need to improve the transparency of the status and</p> <p>14 results of the inspections which I described earlier in</p> <p>15 terms of there being insufficient data since the</p> <p>16 transition to the new management structure has been</p> <p>17 fully implemented to really make any firm conclusions</p> <p>18 about that.</p> <p>19 Again, how do applicants and FDA review staff</p> <p>20 characterize application reviews under the program?</p> <p>21 The last one had to do with communication. This has to</p> <p>22 do with the reviews themselves.</p>
<p>Page 31</p> <p>1 had the highest first-cycle approval rates tended to be</p> <p>2 those that addressed an unmet medical need and</p> <p>3 therefore had priority review.</p> <p>4 The shorter time to first-cycle approval</p> <p>5 tended to be the same applications. Again, those have</p> <p>6 been a priority review which is expected because, of</p> <p>7 course, there's a shorter clock with priority review</p> <p>8 reviews.</p> <p>9 The last couple of questions have to do with</p> <p>10 how applicants and FDA staff characterized the program.</p> <p>11 This slide has to do with how they characterize</p> <p>12 enhanced communication under the program.</p> <p>13 In interviews with applicants and review</p> <p>14 staff, separately, the characterization of program</p> <p>15 communications was largely positive. Interviewees</p> <p>16 typically stated that the communication was excellent</p> <p>17 and constructive.</p> <p>18 They commented that the milestone</p> <p>19 communications facilitate a more holistic discussion</p> <p>20 with the application, provides for a broader FDA input,</p> <p>21 provides for a greater understanding of each party's</p> <p>22 perspectives, and provided a more efficient means of</p>	<p>Page 33</p> <p>1 Again, the characterizations of program</p> <p>2 reviews were largely positive. Folks commented that</p> <p>3 the reviews were very transparent, very predictable,</p> <p>4 very efficient, and that they were especially</p> <p>5 beneficial for applications that require substantive</p> <p>6 discussion and issue resolution throughout the review</p> <p>7 so that the additional communications provided a</p> <p>8 mechanism for doing that.</p> <p>9 Review staff acknowledged that the additional</p> <p>10 program milestones added to the total amount of work</p> <p>11 that's required for any given review but that that</p> <p>12 additional burden is manageable.</p> <p>13 A couple of years ago when we talked about the</p> <p>14 interim report, we communicated a set of findings and</p> <p>15 recommendations. The findings and recommendations for</p> <p>16 this final report are largely similar, except that we</p> <p>17 have removed a few of the findings and recommendations</p> <p>18 because of actions that FDA took midway through the</p> <p>19 program in order to respond to some of the issues that</p> <p>20 we identified at that time.</p> <p>21 One had to do with mid-cycle communication</p> <p>22 procedures, having to do with good communication</p>

<p style="text-align: right;">Page 34</p> <p>1 practices. Those have become pretty much universal in 2 the program. That is no longer a finding or a 3 recommendation that those have been proceeding 4 smoothly.</p> <p>5 The early involvement of a signatory authority 6 is something that has been part of program 7 expectations. Early in the program, we would say that 8 for the most part, that was happening. There were some 9 inconsistencies perceived on some people's part as to 10 whether that was happening with every application. 11 Since there have been reminders of that, the practice 12 has been consistent with program expectations.</p> <p>13 The other comment that we heard was that in 14 some cases, FDA is making attempts -- or plans and 15 attempts to approve applications even earlier than the 16 PDUFA goal date.</p> <p>17 With expedited reviews, when you have a 18 shorter review timeframe, it can be difficult to 19 accomplish all of the program requirements in that 20 short timeframe.</p> <p>21 In response to that, FDA provided refined 22 guidelines for expedited reviews. What we have heard</p>	<p style="text-align: right;">Page 36</p> <p>1 review clock is needed. Again, it has been a positive 2 finding for the program and no action is needed.</p> <p>3 Program implementation has not been resource 4 neutral. Implementation has increased the burden on 5 FDA's primary reviewers, diverting effort from review 6 work to meeting preparation, and sometimes resulting in 7 a need for additional primary review addenda.</p> <p>8 FDA review teams have been able to manage the 9 burden but have noted that additional new burdens 10 might, in some cases, introduce a risk of missed 11 deadlines, compromise the thoroughness of reviews, and 12 impact other non-program work.</p> <p>13 I would stress, again, that as the situation 14 stands, FDA staff have been saying that the extra 15 burden is manageable at this point. This is really 16 just a note. If and when new review process 17 requirements are added that, of course, there would be 18 a need to analyze the associated burden.</p> <p>19 We note this, however, that that would be 20 something that FDA would do in any case. It's not a 21 recommendation that would be endorsed (ph) surprising. 22 It would be something that FDA would do (inaudible).</p>
<p style="text-align: right;">Page 35</p> <p>1 since then is that the refined guidelines have been 2 helpful for keeping up with expedited reviews.</p> <p>3 Now, I'll go into the findings and 4 recommendations that stand for this final report.</p> <p>5 Overall, the program has been successful in enhancing 6 review transparency and communication, so no 7 recommendation needed.</p> <p>8 Overall, the new program milestone 9 communications have enhanced the predictability of 10 reviews by serving as anchor points for applicant and 11 FDA planning and work, and for providing a forum for 12 holistic, multidisciplinary discussion of application 13 status and paths forward to resolve approvability 14 issues promptly, if possible. There's no action 15 needed.</p> <p>16 By providing more opportunity to identify, 17 discuss, and resolve substantive issues during the 18 review, the program has created conditions that enhance 19 the ability of applicants and FDA reviewers to work 20 toward application approval in the first-cycle where 21 possible. This is especially true for applications 22 with substantive but resolvable issues where a full</p>	<p style="text-align: right;">Page 37</p> <p>1 Regardless of sponsor size and experience, 2 many sponsors need more guidance on the format and 3 structure of an application to meet FDA expectations. 4 In some cases, the sponsors have asked that this be 5 done by review division or team and 6 indication/therapeutic area.</p> <p>7 Sometimes sponsors request additional Type C 8 meetings months before the data-orientated 9 pre-submission meeting in order to have greater 10 understanding on format and structure expectations. 11 Some review teams believe that the existing guidance 12 should be sufficient and holding an earlier meeting 13 without data is premature.</p> <p>14 I think that what we hear from sponsors is 15 that sometimes they would like to hear or receive more 16 guidance. The goal here is really to evaluate options 17 for when and how to communicate information about this 18 format and structure of applications.</p> <p>19 There are a lot of ways of accomplishing that. 20 That could include providing internal reviewer aids, 21 increased use of Type C written responses, and so forth 22 to answer questions from the sponsors.</p>

<p style="text-align: right;">Page 38</p> <p>1 Application orientation meetings. In certain 2 CDER review divisions with priority applications where 3 an early action is expected or desired, holding an 4 application orientation meeting within a month or so of 5 submissions has helped acquaint FDA disciplines with 6 application datasets and establish early communication 7 between applicants and FDA about review expectations 8 and perspectives.</p> <p>9 To date, application orientation meetings have 10 been held under pre-specific circumstances. As I 11 mentioned, when an early action is being planned, and 12 it's essentially a priority application.</p> <p>13 Some folks felt that there might be additional 14 applications when an application orientation meeting 15 might be useful as well. The recommendation here is to 16 consider the value of providing information about 17 application orientation meetings to FDA review teams, 18 along with the option to conduct such meetings at the 19 review team's discretion, especially for applications 20 with special designations.</p> <p>21 The application orientation meeting is not 22 necessarily something that is required for every</p>	<p style="text-align: right;">Page 40</p> <p>1 or might not close out that information request in 2 terms of what FDA needs. There might be further 3 questions, further issues, and so forth.</p> <p>4 If FDA and applicants can pursue this option, 5 it needs to be clear that by confirming receipt or 6 affirming the completeness of the information for that 7 particular FDA information request to applicants 8 doesn't necessarily mean that that issue has been 9 resolved.</p> <p>10 With labeling changes, providing explanations 11 and rationales for proposed labeling changes is a good 12 practice for applicants and for FDA review teams.</p> <p>13 This practice has helped both parties 14 understand each other's reasoning, enabling them to 15 respond effectively which then reduces the amount of 16 back and forth required and the time required to 17 complete negotiations on labeling.</p> <p>18 The recommendation here is to include 19 explanations or rationale for proposed label changes, 20 either in written form or more informally as a good 21 practice, to help each side understand what the basis 22 for that is so that they can then respond effectively</p>
<p style="text-align: right;">Page 39</p> <p>1 application, especially standard applications, but it's 2 something to consider as an option where it might be 3 beneficial to the review process. Our understanding is 4 that FDA is proposing this option for PDUFA VI.</p> <p>5 There is a high volume of information request 6 during reviews. What we heard from applicants and 7 review teams is that providing target dates for 8 responses is good practice and that applicants would 9 also benefit from receiving confirmation that the 10 responses are complete.</p> <p>11 The first part of the recommendation is to 12 adopt inclusion of target dates for information request 13 responses as a good practice, which we do see many 14 reviewers doing.</p> <p>15 Second, to develop a simple optional approach 16 for tracking information requests and amendments that 17 can be shared between review teams and applicants.</p> <p>18 One thing that I would note here is that it 19 can be a little bit complicated in terms of describing 20 when a response to information request is satisfactory 21 versus complete because simply responding, providing 22 information in response to an information request might</p>	<p style="text-align: right;">Page 41</p> <p>1 to what the thinking was.</p> <p>2 In terms of inspection information, there's 3 been inconsistent availability or communication of 4 information about the status and results of 5 inspections, hindering review transparency and 6 predictability, both internally within FDA and between 7 FDA and applicants.</p> <p>8 Again, I can refer back to my earlier 9 discussion in terms of to what extent the changes in 10 management of inspections is, changing that, the 11 insufficient data to make any firm conclusions about 12 that.</p> <p>13 Another note that I'd like to make is that in 14 some cases, there are legal constraints around 15 communicating the status of results of inspections with 16 applicants.</p> <p>17 For NDAs, a lot of times, applicants are using 18 contact organizations, and there are legal issues 19 around disclosing the results to the applicant as 20 opposed to the site. With BLAs, more of those 21 facilities are applicant-owned, and so that tends to 22 come up less.</p>

<p style="text-align: right;">Page 42</p> <p>1 The recommendation is to examine inspection 2 information flows and communication channels with the 3 aim of identifying improvements, and FDA is conducting 4 such an examination.</p> <p>5 All right. That's it. Thank you.</p> <p>6 FDA Perspective</p> <p>7 MS. HAFIZ: Thank you, Valerie. Now, we'll 8 move into our panel session. The first panel will be 9 made up of FDA staff and will focus on providing FDA's 10 experience and perspectives on the program. If we can 11 have our FDA panelists come up to the table.</p> <p>12 Once all the FDA panelists have provided their 13 perspectives, we'll ask that they take a seat in the 14 front row so our industry stakeholders can come up. 15 FDA panelists, if you could introduce 16 yourselves before you begin.</p> <p>17 MR. FREY: Good morning. I'm Patrick Frey, 18 chief of staff in the Office of New Drugs. I'll start 19 off with comments on the FDA side.</p> <p>20 Just to provide a little bit of a historical 21 context first, the NME review program renegotiated this 22 2010, starting in 2010, and that wasn't (ph) coming off</p>	<p style="text-align: right;">Page 44</p> <p>1 program during PDUFA V and then figure out, do we want 2 to discontinue it or not?</p> <p>3 Those discussions continued, but then there 4 was a sense that if we kept calling it a pilot program, 5 maybe "pilot" would be thought synonymously in terms of 6 it being temporary, and there would be a lack of 7 commitment to it.</p> <p>8 We dropped the "pilot" term at the time and 9 recognized then that both FDA and industry were 10 committed to the program and that it would be assessed 11 twice during PDUFA V. Then we would figure out during 12 PDUFA VI discussions what we wanted to do with the 13 program.</p> <p>14 I think the outcome that we've seen so far of 15 the NME program, and the interim assessment, and in the 16 final assessment has pretty much been a good report 17 card for both the FDA and for industry.</p> <p>18 Notably, during the interim assessment, it was 19 just that the data was only enough at the interim 20 assessment to show that we had a statistically 21 significantly higher first-cycle approval rate for 22 priority applications.</p>
<p style="text-align: right;">Page 43</p> <p>1 of the first two years of PDUFA IV, 2008 and 2009.</p> <p>2 At that time, the new drug review process was 3 really challenged mainly because of the new complex 4 authorities we got at FDA (inaudible) that we had to 5 implement, figure out, in a very short span of time, 6 and then get used to them as well.</p> <p>7 That was the context of our discussions for 8 PDUFA V that led to the NME review program. I think at 9 that time, there was a shared belief that by 10 establishing communication points during the review 11 process and lengthening the review time for FDA for 12 (inaudible) applications, any NDAs or original BLAs 13 that we might see an increase in the efficiency of the 14 (inaudible) cycle.</p> <p>15 No one was really certain at that time that it 16 would do the trick. We spoke of the program in terms 17 of it being a pilot actually. The minutes reflect 18 this.</p> <p>19 For a number of weeks during those PDUFA V 20 discussions, we were talking about this being a pilot 21 program. There was even discussion at the time that 22 maybe we would look at an interim assessment of the</p>	<p style="text-align: right;">Page 45</p> <p>1 Then for the final assessment, we've had 2 enough experience with standard applications to say 3 that, hey, across this program, when we compare it to 4 the baseline, we have a better run (ph) and a more 5 efficient first-cycle review process.</p> <p>6 I think the NME program in PDUFA V formalized 7 some practices that existed in some parts of our new 8 drug review program and served to then make that a 9 fully implemented component of new drug review. This 10 is kind of baked into our review process now.</p> <p>11 I think that the PDUFA VI agreement that 12 published last summer proposes just some tweaks at the 13 edges, that the program is viewed as a success. That's 14 how the discussions were characterized during PDUFA VI, 15 and we made some small changes to make it a little bit 16 more flexible.</p> <p>17 If a review team and the applicant have a 18 different way that they like to do business during the 19 review of a marketing application, they can do that as 20 long as they reach agreement on how they're going to 21 interact and communicate during the review of that 22 application.</p>

<p style="text-align: right;">Page 46</p> <p>1 I think from my own perspective, the PDUFA 2 program has essentially spent 25 years now developing, 3 refining, continuously improving a review process such 4 that now, we're making marginal changes here and there 5 which we did in PDUFA VI. I think we'll continue doing 6 that going forward. Major changes to the review 7 process just didn't happen in PDUFA VI. 8 When we talk about getting drugs to patients 9 faster, I think now, the move is more to look at the 10 full development timeline. Some of that was introduced 11 in PDUFA V when we saw initiatives related to rare 12 diseases, and biomarkers, and pharmacogenomics. Most 13 of those were expanded then in PDUFA VI. 14 I think while the practices and principles of 15 continuous improvement dictate that we continue to look 16 at the review process to make sure it is run as 17 efficiently as possible, now, I think there seems to be 18 general agreement within the community that we operate 19 in that getting drugs to patients faster now is about 20 looking at the full development timeline and focusing 21 energies there. 22 I want to thank ERG. They've been with us</p>	<p style="text-align: right;">Page 48</p> <p>1 Evaluation I who oversees the divisions of 2 cardiovascular and renal products, psychiatry, and 3 neurology. 4 I take it you want my reflections now. My 5 perception of the program is positive. I wouldn't even 6 say generally positive. It's positive. I don't have 7 any reservations about the program. 8 I think it's been a success. I think that 9 giving extra transparency to industry is a good idea. 10 In contradistinction to last-minute surprises that 11 can't be remediated within the timeframe of a goal 12 date, that was not a good idea, and this is definitely 13 better. 14 I have one area I'd like to comment on 15 specifically. I know the program pretty well because 16 one of the problems I had was I had to provide a 17 presentation of the program to all three of my 18 divisions. I had to write a talk and do three one-hour 19 talks to my three divisions explaining the program. 20 One of the things that was in the program that 21 we haven't discussed this morning was the completeness 22 of applications at the time of submission.</p>
<p style="text-align: right;">Page 47</p> <p>1 since 2012, summer of 2012, doing a very good job. 2 Implementing the evaluation of the program as it was 3 envisioned during PDUFA V discussions. During those 4 discussions, we talked to industry about the fact that 5 we felt we would need the contractors to basically be 6 living with us. That's exactly what happened, being in 7 person, attending all these meetings, witnessing the 8 interactions so that we could get the best evaluation, 9 the best feedback about the program. 10 I think we all recognized even during PDUFA V 11 discussions, that was really going to be qualitative 12 feedback that came from FDA review teams and from 13 applicants in terms of how the interactions went. 14 Do you feel like the time spent with FDA 15 during the review process was a good use of time? I 16 think that the evaluation results speak pretty well to 17 that. 18 I'll stop there and turn it over to my 19 colleagues. 20 DR. UNGER: I'm Ellis Unger. I'm director of 21 Office of Drug Evaluation I in the Office of New Drugs. 22 I'm a signatory authority in the Office of Drug</p>	<p style="text-align: right;">Page 49</p> <p>1 One of the things that we were supposed to 2 have obtained in the program was that all submissions 3 were supposed to be complete. We were to threaten 4 applicants that if they're submission was not complete 5 that we could refuse to file it, and we would. 6 We didn't talk about this, and you don't (ph) 7 show a slide on refused -- I don't think that there 8 were a larger number of refused-to-file applications. 9 There was -- I will call it a drift in the 10 three divisions that I oversee in that at the 11 beginning, we tried to be dogmatic about this. We told 12 the company, yes, you have to be complete or we won't 13 file your application. 14 Basically, all three of the divisions' 15 directors in ODE I wanted to be flexible, and so they 16 all said, well, look, that's ridiculous. If they need 17 to submit something in two or three weeks, that's okay. 18 That's what, in fact, happened. I think the 19 program was a success, but I think there may be a 20 disconnect now between what's actually written in the 21 program which is no flexibility to be extended here 22 versus what we did in practice.</p>

<p style="text-align: right;">Page 50</p> <p>1 Patrick, you're probably the expert on what's 2 in the program. I don't think the program was changed. 3 I mean I never got a memo saying, we can be more 4 flexible now. I think there could be a disconnect that 5 maybe we should try to fix. 6 I think flexibility is a good idea. I don't 7 think that part of the program was needed, that this 8 draconian, you better submit something that's complete 9 or we refuse to file. 10 Maybe you want to say something? 11 MR. FREY: We did institute a bit of 12 flexibility for PDUFA V to allow for late submission, 13 "late" defined as during the first 30 days after 14 original receipt of the application, late submission of 15 minor components of the application. 16 There are a small number of examples of what 17 is a minor component of an application in the 18 commitment letter. One thing that we didn't want to 19 see was that at month 3, 4, or 5 that a whole new study 20 comes in that we have to evaluate. 21 That was the extent of the flexibility that we 22 established in the program, and that does not change in</p>	<p style="text-align: right;">Page 52</p> <p>1 took out this header because for whatever reason. 2 Maybe other people could comment on that. 3 In summary, I'll say what I already said which 4 is I think that the program has been a success. I 5 don't have any reservations about it. It does require 6 more effort on the part of our reviewers. 7 If we save ourselves a second cycle or a third 8 cycle, that's huge savings right there. I think we all 9 appreciate that this has been a positive change. 10 I'll stop. 11 DR. SMITH: My name is Jim Smith. I'm the 12 deputy division director for the Division of Metabolism 13 and Endocrinology Products in OND in CDER. 14 I would also echo that I think in general, the 15 program has been very positive. I think that 16 obviously, communication and transparency are the key 17 objectives. I think that we were a division that was 18 not -- as a general practice, our division did not 19 hesitate to communicate even before the program with 20 applicants regularly throughout a review cycle. 21 I don't know that there was a major shift in 22 culture or practice. Formalizing the communication</p>
<p style="text-align: right;">Page 51</p> <p>1 PDUFA VI. 2 DR. UNGER: In terms of some of the other 3 things that seemed to be on the table right now, one is 4 keeping track of the information requests, which seems 5 to be a reasonable idea. 6 Although, as Valerie said, our concept of a 7 complete response to an information request could be 8 different from a company's. Answering the question 9 versus making reviewers happy can be two different 10 things. It's something, I think, that might be worth 11 trying to put some effort into down the line. 12 In terms of labeling negotiations, I think 13 there is some variation from division to division, and 14 there probably some from office to office in terms of 15 the actual nitty gritty negotiations that take place. 16 I know most of my divisions put -- we work 17 within Microsoft Office Word, and we have track 18 changes, and we also have balloons where we say, Dear 19 Applicant, we changed this for such and such a reason. 20 I don't know if the industry is looking for a 21 more explicit explanation or some other vehicle for 22 explanation, but we do try to put in a label that, we</p>	<p style="text-align: right;">Page 53</p> <p>1 with respect to the mid-cycle and late-cycle 2 communications, I think, does reduce some heterogeneity 3 among different practices even within the division. 4 I think what it also does is by having formal 5 touchpoints with the applicant, we have found it 6 particularly useful in complex applications where there 7 may be a multitude of consultants perhaps across 8 centers. 9 Having some of those consultants at the table 10 at a mid-cycle communication or a late-cycle 11 communication, I believe, instills an extra sense of 12 ownership to the review, to the consultants as well and 13 really integrates them into the primary team. 14 We have certainly had -- I mean I'm speaking 15 anecdotally. We've certainly had examples of reviews 16 where early involvement from colleagues in CDRH with 17 device-related issues, especially for combination 18 products, and the fact that we will get their advice 19 early before the mid-cycle has been helpful and has 20 definitely led to first-cycle approvals. 21 Talking to Ellis' flexibility, we've had 22 devices that were substantially altered during the</p>

<p style="text-align: right;">Page 54</p> <p>1 review cycle but were still able to be reviewed in time 2 enough so that they could be approved. Definitely, 3 that has helped.</p> <p>4 Regardless of the complexity of the 5 application, it helps reviewers prioritize their 6 reviews because they don't want to have a conversation 7 with an applicant at the mid-cycle, having not hit the 8 major potential showstoppers, if you will, and then 9 have to surprise the applicant later in the review 10 cycle. I think it does help to that regard.</p> <p>11 We've had some experience with other 12 pre-submission activities that under PDUFA VI would be 13 optional; that is, on several occasions, we have 14 granted and have given written responses for Type C 15 meetings for just data structure, application 16 structures, so not a data-driven meeting.</p> <p>17 We've recognized that applicants can spend a 18 fair amount of time programming from the technical 19 aspects long before a pre-NDA or a pre-BLA meeting. If 20 we have those interactions early, then we're more 21 likely to get a package that we like to review at the 22 pre-NDA and pre-BLA. We've found that to be helpful.</p>	<p style="text-align: right;">Page 56</p> <p>1 late-cycle meeting is so close to advisory committee 2 meetings that if it's all timed properly that pretty 3 much every has their meeting ready to go so that's it's 4 a little bit late to get involved in that.</p> <p>5 But as I said, it isn't resource-neutral. I 6 think that these meetings can be difficult. Even on 7 our project managers, they can be very difficult to 8 schedule, depending on the number of folks involved in 9 the signatory schedule and the number of bodies that 10 have to be in a room.</p> <p>11 I think early on in PDUFA V, we made these 12 meetings more laborious than they needed to be. Since, 13 we've learned to stream line.</p> <p>14 I think I'll go ahead and stop there. In 15 summary, I think that hopefully -- and it sounds like, 16 based on the final assessment, I think that there is 17 some agreement on both sides that communication and 18 transparency has increased. Certainly, I think that 19 that's what we felt at the division level as well.</p> <p>20 DR. JONECKIS: I'm Chris Joneckis. I'm the 21 associate director for review management, Center for 22 Biologics. I'm responsible for implementing all the</p>
<p style="text-align: right;">Page 55</p> <p>1 With regard to the pre-submission meetings and 2 the classical pre-NDA and pre-BLA meetings, I think 3 that all of the enhanced communication and transparency 4 that I believe has filtered down into the primary 5 review staff and is becoming part of the culture is 6 making folks take an increased ownership at those early 7 pre-submission stages about designing the application 8 that they would like to review instead of only reacting 9 to the application that comes in the door.</p> <p>10 That's challenging when -- obviously, industry 11 has to do it all the time and take their best guess 12 about what we want to see. It turns the tables a 13 little bit by having our reviewers take some ownership 14 in the application that they'd like to see, but all in 15 all, I think that's a good thing.</p> <p>16 We found the late-cycle meetings be a little 17 bit less helpful. Obviously, if there were late 18 showstoppers, I think that that could be a very useful 19 meeting.</p> <p>20 Applications that are destined for an advisory 21 committee, I think the hope was the late-cycle meeting 22 to kind of help coordinate that. In reality, the</p>	<p style="text-align: right;">Page 57</p> <p>1 user fees in the center.</p> <p>2 The program assessment that you saw was a 3 combined CDER/CBER data. If you look at the CBER 4 numbers, they pretty much overall have the same 5 outcomes and observations that Valerie presented.</p> <p>6 We have increased per cycle rates and 7 decreased time to approval for priority over standard, 8 in both categories as well. I think most of the 9 patterns and attributes and things generally hold.</p> <p>10 We have some smaller numbers, so it may be a 11 little bit harder to make some of those observations. 12 In general, we've seen those that that's pretty much 13 the case.</p> <p>14 The impact of the program, I'd like to say 15 that it's built on longstanding traditions of what 16 we've done at CBER and tried to have intensive 17 communications, a lot of work during development. We 18 have a lot of work from products for years and still 19 do.</p> <p>20 I think in the case that when the program came 21 along, for folks who are doing all that, that was 22 great. Perhaps for some that weren't, this made it</p>

<p style="text-align: right;">Page 58</p> <p>1 even better.</p> <p>2 It took a lot of the best practices that I</p> <p>3 think existed across the centers and made that a little</p> <p>4 bit more formalized, a little more process oriented and</p> <p>5 such in CBER.</p> <p>6 I'll give you an example. We took the</p> <p>7 mid-cycle communications. We've always had mid-cycle</p> <p>8 internal meetings for years now. What we did is we</p> <p>9 said, okay, we're going to have a reviewer's report.</p> <p>10 We had all the reviewers complete a very short</p> <p>11 targeted-focus reviewer report: what's the status of</p> <p>12 our reviews, what's the status of the information</p> <p>13 request from the industry, do I have hold issues, do I</p> <p>14 have issues that can't be resolved in the first-cycle?</p> <p>15 We did that, and at first, a lot of people</p> <p>16 complained about it. We kept it short, very focused,</p> <p>17 and it actually facilitated over all the internal</p> <p>18 mid-cycle meeting. It made it a very more productive,</p> <p>19 efficient type of meeting where things could get</p> <p>20 discussed and get resolved in, say, an hour or an hour</p> <p>21 and a half and making any kind of course corrections</p> <p>22 that we needed.</p>	<p style="text-align: right;">Page 60</p> <p>1 The approach we take at CBER is sort of a</p> <p>2 continual assessment. We make assessments at the</p> <p>3 beginning just to determine what inspections have to be</p> <p>4 scheduled or not.</p> <p>5 After our inspection, we work through our</p> <p>6 EIRs, our establishment inspection reports, issues that</p> <p>7 may come up on the 483s and such to try to resolve</p> <p>8 those.</p> <p>9 We don't make a final determination on any of</p> <p>10 our facilities until the last 30 days before approval</p> <p>11 because it's not just the site we're looking at; it's</p> <p>12 the overall compliance history of that site, and other</p> <p>13 things may arise that can affect that.</p> <p>14 To say that we make the determination in the</p> <p>15 last 30 days is also going to skew the data. We really</p> <p>16 don't have a site determination equivalent that, I</p> <p>17 think, CDER has evolved to over this process. Again,</p> <p>18 it's a little bit different.</p> <p>19 We do work very extensively with manufacturers</p> <p>20 to try to resolves those issues that are outstanding to</p> <p>21 get them to an approvable facility, especially in the</p> <p>22 case of public health needs, breakthrough therapy</p>
<p style="text-align: right;">Page 59</p> <p>1 Again, I think the impact of the program was</p> <p>2 to formalize a lot of the good practices and principles</p> <p>3 that we've had. Overall, I think the reviewers like</p> <p>4 it.</p> <p>5 RPMs love it. They like that structure. They</p> <p>6 like the focus. Anything that helps them manage, they</p> <p>7 like a lot. They weren't all converts in the</p> <p>8 beginning, but over time, I think that's where they</p> <p>9 are.</p> <p>10 A couple of comments on inspection,</p> <p>11 inspections for biologics represents some unique</p> <p>12 challenges as Valerie, I think, had tried to indicate.</p> <p>13 One example is just for the manufacturer of</p> <p>14 the drug substance or the active pharmaceutical. The</p> <p>15 facility typically has to be a manufacturer. Say, if</p> <p>16 you're manufacturing that product or a similar product,</p> <p>17 that, off the bat, changes when you're going to be able</p> <p>18 to have that inspection.</p> <p>19 That requires a lot of pre-discussion with the</p> <p>20 company well before -- sometimes even before the</p> <p>21 pre-BLA meeting to schedule that. That's going to</p> <p>22 start to change the data that you see.</p>	<p style="text-align: right;">Page 61</p> <p>1 products, shortage products, and thing of that nature.</p> <p>2 That can be literally working to the last day or so</p> <p>3 before approval with some of these companies.</p> <p>4 The only other thing I guess I'd like to</p> <p>5 mention, as I think Ellis and others may have said,</p> <p>6 it's a two way street. Enhanced communication,</p> <p>7 enhanced transparency, predictability is all important.</p> <p>8 I've been at CBER way too long now. We used</p> <p>9 to like to say, no surprises, and I actually heard</p> <p>10 Ellis said that. I don't think we see as many</p> <p>11 surprises as much anymore.</p> <p>12 I think that's sort of evolved. I think the</p> <p>13 programs helped to get rid of those things. When we do</p> <p>14 see surprises, it's often from a more naïve company</p> <p>15 maybe that's not as familiar with the process and</p> <p>16 talking things through.</p> <p>17 It is important that you have good quality</p> <p>18 applications, and that really does make it a lot</p> <p>19 easier. That can be everything from the discussion of</p> <p>20 the format, are you using the appropriate electronic</p> <p>21 format, are you using appropriate data standards</p> <p>22 formats to a lot of things. That really facilitates</p>

<p style="text-align: right;">Page 62</p> <p>1 the review process.</p> <p>2 That's pretty much it. I think moving into</p> <p>3 PDUFA VI, like Patrick said, there are minor tweaks and</p> <p>4 things. It gives a lot of additional flexibility for</p> <p>5 the agency and the applicant to determine what flavor</p> <p>6 really suits their purpose. I think that's actually a</p> <p>7 good thing.</p> <p>8 We found in PDUFA V that the late-cycle</p> <p>9 meetings really weren't productive in a lot of cases,</p> <p>10 and we didn't need them. We never denied them. If the</p> <p>11 company wanted to have them; we had them.</p> <p>12 As it evolved, we just said, there's no reason</p> <p>13 to have a late-cycle meeting. If it can be agreed by</p> <p>14 mutual agreement not to have them, we didn't.</p> <p>15 Sometimes we turned those into labeling</p> <p>16 meetings; sometimes we couldn't because we still</p> <p>17 weren't there yet with the labeling. Again, we didn't</p> <p>18 have any real show-stopping issues.</p> <p>19 Again, I think building in that flexibility</p> <p>20 will give us even additional benefits. Thanks.</p> <p>21 MR. ISER: Good morning. I'm Bob Iser. I'm</p> <p>22 the director of the Office of Process and Facilities in</p>	<p style="text-align: right;">Page 64</p> <p>1 transition.</p> <p>2 Also, we saw that there were areas where we</p> <p>3 could be more communicative, more transparent</p> <p>4 internally and externally. We've been working over the</p> <p>5 past several years along with our colleagues in RA and</p> <p>6 then throughout CDER, again, as part of the whole</p> <p>7 program alignment activities that -- you know, where</p> <p>8 can we make our process more effective, more efficient,</p> <p>9 where can we communicate better, what are the clear</p> <p>10 roles and responsibilities in managing pre-approval</p> <p>11 inspections, and having really good discussions</p> <p>12 throughout CDER and RA, coming together with an</p> <p>13 agreed-upon concept that we can then operationalize</p> <p>14 which I think is very promising.</p> <p>15 One of the other things we did was we said,</p> <p>16 well, let's separate out surveillance, or the general</p> <p>17 GMP inspections, from pre-approval inspections. That</p> <p>18 happened soon after the standup of OPQ.</p> <p>19 Some of the data that you're looking at is a</p> <p>20 surveillance inspection maybe not triggered by the</p> <p>21 application but triggered on time since last</p> <p>22 inspection. There are different reasons why we might</p>
<p style="text-align: right;">Page 63</p> <p>1 OPQ within CDER.</p> <p>2 A couple of things I wanted to react on. I'll</p> <p>3 focus most of my topics on inspections when it comes to</p> <p>4 CDER and then some of the things that we may be doing</p> <p>5 to address some of the observations that were made as</p> <p>6 this report was put together.</p> <p>7 I'm also encouraged by the recommendations,</p> <p>8 the observations that were made. I think that it shows</p> <p>9 a lot of areas where we could still improve, and I</p> <p>10 think we are starting to improve within our office, and</p> <p>11 throughout CDER, and throughout the FDA.</p> <p>12 I wanted to touch upon a couple of things that</p> <p>13 were noted in the presentation. The Office of</p> <p>14 Pharmaceutical Quality and the office I'm in stood up</p> <p>15 in January of 2015. At that time, we shifted the</p> <p>16 management of pre-approval inspections from the Office</p> <p>17 of Compliance to my office, the Office of Process and</p> <p>18 Facilities.</p> <p>19 With that came some transition period.</p> <p>20 Luckily, the people that came into that office were</p> <p>21 people who were doing that work within the Office of</p> <p>22 Compliance for the most part. That helped in the</p>	<p style="text-align: right;">Page 65</p> <p>1 go out and inspect.</p> <p>2 One of the reasons to separate also was the</p> <p>3 fact that time since last inspection as a standalone</p> <p>4 trigger is not appropriate risk-based decision to</p> <p>5 trigger a pre-approval inspection for an application</p> <p>6 coming in.</p> <p>7 The surveillance inspection, while still</p> <p>8 informative to the approvability or non-approvability</p> <p>9 of an application, if there's a surveillance inspection</p> <p>10 happening, that doesn't mean we have to hold up an</p> <p>11 action on an application.</p> <p>12 I think that's important, and that'll be</p> <p>13 something that I think we'll all see the impact of that</p> <p>14 a lot more of as we gather more data and as we have</p> <p>15 that process in place.</p> <p>16 I wanted to also highlight a couple of things</p> <p>17 that they came up in the recommendations. This should</p> <p>18 not be any surprise as I bring these up.</p> <p>19 A look in (ph) sponsors or the facilities that</p> <p>20 are communicating with us do, from a sponsor</p> <p>21 perspective, obviously, complete, accurate information</p> <p>22 coming in in the submission. It was highlighted about</p>

<p style="text-align: right;">Page 66</p> <p>1 complete submissions.</p> <p>2 Also, if there's any opportunities to do that</p> <p>3 before the NDA comes in, especially for these priority</p> <p>4 applications, have that information that's complete and</p> <p>5 accurate because it really, really impacts us if we're</p> <p>6 doing a more in-depth review or if we're doing an</p> <p>7 inspection and find another facility that was not</p> <p>8 listed in the application. Then we'd have to make a</p> <p>9 decision then and there, do we go and inspect that</p> <p>10 facility depending on the impact on the quality of that</p> <p>11 product.</p> <p>12 Responsiveness of the facilities as we're</p> <p>13 going through and doing an inspection and then</p> <p>14 following up on that inspection, making sure that we</p> <p>15 get good responses from the facilities that it's done</p> <p>16 in those very tight timeframe so that we can make that</p> <p>17 final assessment decision.</p> <p>18 And understanding, as I mentioned, that if</p> <p>19 things happen during the review cycle or during the</p> <p>20 inspection itself or we're seeing additional</p> <p>21 facilities, understand from the sponsor's perspective</p> <p>22 that that will impact the final assessment that we're</p>	<p style="text-align: right;">Page 68</p> <p>1 Thank you. Now, we're ready to begin our next</p> <p>2 panel session, focused on industry's perspectives and</p> <p>3 experience with the NME program.</p> <p>4 Panelists, if I could just ask you to</p> <p>5 introduce yourselves before you begin speaking. Thank</p> <p>6 you.</p> <p>7 DR. VERESHCHAGINA: Good morning, everybody.</p> <p>8 Lucy Vereshchagina. I'm vice-president of Science and</p> <p>9 Regulatory Advocacy for Pharmaceutical Research and</p> <p>10 Manufacturers of America, PhRMA for short.</p> <p>11 As I mentioned, I'm speaking on behalf of</p> <p>12 PhRMA this morning. PhRMA represents the country's</p> <p>13 leading innovative biopharmaceutical research and</p> <p>14 biotechnology companies which are devoted to</p> <p>15 discovering and developing medicines that enable</p> <p>16 patients to live longer, healthier, and more productive</p> <p>17 lives.</p> <p>18 PhRMA member companies are leading the way in</p> <p>19 search of new cures, investing in estimated</p> <p>20 \$58.8 billion in 2015 alone in the discovery and</p> <p>21 development of new medicines.</p> <p>22 On behalf of PhRMA, thank you for the</p>
<p style="text-align: right;">Page 67</p> <p>1 doing, that overall facility assessment that was noted.</p> <p>2 I'll wrap up with saying that -- well, I think</p> <p>3 it goes without saying that we're committed in FDA to</p> <p>4 be as transparent as we can. There are some</p> <p>5 limitations when it comes to the facility information,</p> <p>6 but I think we all benefit from being transparent and</p> <p>7 openly communicate where we can about the facility</p> <p>8 status, the inspection status, and that there will be</p> <p>9 times where we make a decision based on the fact that</p> <p>10 this facility may or may not be compliant or may be</p> <p>11 doing towards compliance, but we would hold up an</p> <p>12 action until we can get resolutions so that we can get</p> <p>13 that approval to benefit the American public as opposed</p> <p>14 to just reacting by sending a complete response, that</p> <p>15 that depends on responsiveness and also what we found</p> <p>16 in those facilities.</p> <p>17 Thanks again for giving me an opportunity to</p> <p>18 react.</p> <p>19 Industry Perspective</p> <p>20 MS. HAFIZ: Thank you. If can have our FDA</p> <p>21 panelists move to the front row the industry panelists</p> <p>22 can come up.</p>	<p style="text-align: right;">Page 69</p> <p>1 opportunity to provide comments on the independent</p> <p>2 final assessment of the review program for NME NDAs and</p> <p>3 original BLAs.</p> <p>4 Over the course of PDUFA V, the program has</p> <p>5 been successfully implemented by the agency as intended</p> <p>6 and outlined in the PDUFA V performance goals letter.</p> <p>7 The program has achieved its goal of improving</p> <p>8 the effectiveness of the first-cycle review process to</p> <p>9 NDAs and BLAs. First-cycle approval rates reported in</p> <p>10 the final assessment report for the program are higher</p> <p>11 than they reported in the interim assessment with the</p> <p>12 overall first-cycle approval rates at almost</p> <p>13 80 percent.</p> <p>14 Overall, FDA sustained progress in the NME</p> <p>15 review process during PDUFA V, including the time for</p> <p>16 review and especially in the first-cycle approval rates</p> <p>17 which, in 2015, increased to 95 percent.</p> <p>18 The final assessment determined that the</p> <p>19 differences in the first-cycle approval rates between</p> <p>20 the baseline and the program are statistically</p> <p>21 significant for both priority and standard</p> <p>22 applications.</p>

<p style="text-align: right;">Page 70</p> <p>1 PhRMA supported the establishment of the</p> <p>2 program in PDUFA V and will look forward to working</p> <p>3 with the agency as the program continues in PDUFA VI.</p> <p>4 PDUFA VI enhances the agency's ability to</p> <p>5 review innovative treatments and preserve the current</p> <p>6 eight months for a priority and 12 months for a</p> <p>7 standard review timelines for NDAs and BLAs.</p> <p>8 As a result, patients in the United States</p> <p>9 will continue to benefit from timely access to safe and</p> <p>10 effective new medicines.</p> <p>11 I'd like to make just a few brief comments on</p> <p>12 a few key issues in the final assessments. With regard</p> <p>13 to the program resources, similar to interim</p> <p>14 assessment, final reports states that the program has</p> <p>15 not been resource-neutral and has increased the burden</p> <p>16 on FDA primary reviewers and regulatory project</p> <p>17 managers.</p> <p>18 The final review also states the review teams</p> <p>19 have been able to adapt to the new program milestones</p> <p>20 and goals and does acknowledge the dedication of FDA</p> <p>21 review staff to meet the goals despite the hiring</p> <p>22 challenges that the agency faced in the recent years.</p>	<p style="text-align: right;">Page 72</p> <p>1 to submission of relatively small amount of information</p> <p>2 in response to an information request.</p> <p>3 With regard to inspections, we agree that the</p> <p>4 final assessment finding that inconsistent availability</p> <p>5 and communication of information about the status and</p> <p>6 results of inspection has hindered review timeline</p> <p>7 transparency and predictability.</p> <p>8 The final report states that only 46 percent</p> <p>9 of program applications received inspection that were</p> <p>10 completed within program timelines. For those that</p> <p>11 were not completed within the program timelines, the</p> <p>12 majority were due to the late completion of GMP</p> <p>13 inspections.</p> <p>14 PhRMA is pleased that the agency is</p> <p>15 undertaking review of inspection information flow,</p> <p>16 considering that the final report states that the</p> <p>17 applications receiving on time inspection received</p> <p>18 first-cycle approval over one and a half months earlier</p> <p>19 than those applications that did not receive on time</p> <p>20 inspections.</p> <p>21 With regard to review communications, the</p> <p>22 success of the program relies on effective two way</p>
<p style="text-align: right;">Page 71</p> <p>1 PDUFA VI helps to ensure that the FDA's</p> <p>2 resource and staff to support the regulatory review and</p> <p>3 approval process for new medicines, that they're</p> <p>4 scientifically sound, and efficient, and predictable.</p> <p>5 With regard to PDUFA goal extensions and major</p> <p>6 amendments that were mentioned this morning, according</p> <p>7 to final report, almost 23 percent of applications in</p> <p>8 the program received a goal extension of three months</p> <p>9 due to major amendment.</p> <p>10 Considering that the program application must</p> <p>11 be completed at the time of submission as agreed to by</p> <p>12 sponsor and FDA, and the increased program</p> <p>13 communication are intended to identify and resolve</p> <p>14 issues early in the review process, we would like to</p> <p>15 better understand the agency's rationale for</p> <p>16 (inaudible) *1:29:13 responses to information request</p> <p>17 as major adjustments and the timing of information</p> <p>18 requests that result in major amendments.</p> <p>19 We recommend that the FDA explore ways to</p> <p>20 enhance the consistency across review divisions with</p> <p>21 regard to major amendments, particularly as it relates</p> <p>22 to decreasing the frequency of goal date extensions due</p>	<p style="text-align: right;">Page 73</p> <p>1 communications between FDA and the sponsor throughout</p> <p>2 the drug development and regulatory review process.</p> <p>3 We definitely appreciate FDA's effort to be</p> <p>4 responsive to feedback emerging from early experience</p> <p>5 with the program and the agency's implementation of</p> <p>6 better practices in real time.</p> <p>7 We're pleased to see that the final report</p> <p>8 states that the agency addressed mid-cycle</p> <p>9 communication and signatory authority issues raised in</p> <p>10 the interim assessment by implementing refined</p> <p>11 guidelines.</p> <p>12 We encourage the FDA to continue promoting</p> <p>13 policies and procedures that ensure that robust</p> <p>14 engagement occurs consistently at both mid-cycle and</p> <p>15 the late-cycle meetings.</p> <p>16 In conclusion, we appreciate the agency's</p> <p>17 effort to meet the program's goal as outlined in</p> <p>18 PDUFA V and would like to thank FDA for bringing all</p> <p>19 stakeholders today an efficient and effective review</p> <p>20 process critical for ensuring timely patient access to</p> <p>21 innovative safe and effective new drugs and biologics.</p> <p>22 We look forward to working with FDA and all</p>

<p style="text-align: right;">Page 74</p> <p>1 stakeholders as the program continues in PDUFA VI. 2 Thank you. 3 DR. METCALF: Good morning. My name Rob 4 Metcalf, and I'm the vice-president of Diabetes 5 Clinical Development and Clinical Transformation at 6 Eli Lilly and Company. 7 I'm also the past vice-president of Global 8 Regulatory Affairs, and in that role, did have the 9 opportunity to oversee submission applications to the 10 FDA under the program. 11 Thank you very much, on behalf of Eli Lilly, 12 to be here to comment today on the program. Thank you 13 to the Eastern Research Group and Valerie for the 14 excellent presentation that you did today. 15 I think that just reemphasizes the overall 16 success of the program. Increasing our first approval 17 rates to 80 percent over the baseline certainly 18 exemplifies the overall goals of continuing to ensure 19 timely delivery of safe, effective, and high quality 20 new medicines to patients in need. 21 Certainly, this has been Lilly's experience as 22 well. Overall, we view the program as being very</p>	<p style="text-align: right;">Page 76</p> <p>1 facilitated the review process, have been beneficial in 2 aligning the FDA and the sponsor, Lilly, to lead to 3 quicker resolution of issues. 4 Lilly views communications during the 5 pre-submission meetings as critically important to 6 overall review success. The communications allow for 7 better planning of application content to ensure a 8 complete application, but more importantly, help us to 9 work with the FDA on the nuances of applications. As 10 Jim pointed out, some of those, at times, can be 11 challenging to work through. 12 We have found that having more than one 13 meeting with the FDA in advance of an application is 14 beneficial, and that's been pointed out in the Eastern 15 Research Group comments and feedback that you've 16 received. 17 We'd encourage the FDA to continue to use this 18 paradigm when working with sponsors on applications, 19 particularly those applications that may be more 20 complex in nature. As Valerie pointed out, there may 21 be different paradigms to do that, but we've seen that 22 as valuable as a sponsor.</p>
<p style="text-align: right;">Page 75</p> <p>1 successful in helping to meet those goals and 2 objectives. 3 I was honored to be a member of the PDUFA VI 4 negotiating team that negotiated the commitment letter 5 that hopefully will become effective by the end of Q3 6 this year. 7 In that letter, we institutionalized many 8 components of the program, and that demonstrated our 9 company's support for the excellent elements that we 10 saw in PDUFA V, moving them into and making them 11 permanent as part of PDUFA VI. 12 As I've said, our overall Lilly experience 13 with the program has been very positive. We've seen 14 significantly improved two-way communication with 15 review staff as compared to our PDUFA IV experiences. 16 In particular, the mid cycle meetings and 17 late-cycle meetings have facilitated a higher level of 18 review transparency as compared to previous programs. 19 Furthermore, we've seen a much higher level of 20 openness by review staff to ad-hoc communications, 21 either through teleconferences, rapid email exchanges 22 and occasional face-to-face meetings that have</p>	<p style="text-align: right;">Page 77</p> <p>1 Lilly has derived notable value in meetings 2 with the FDA team during both the mid-cycle and 3 late-cycle review meetings. The holistic 4 multidisciplinary discussion of application status 5 during those meetings gives insight into the timeline 6 for FDA's review and action and helps focus attention 7 of the key players on resolving review issues and 8 concerns. 9 This increased level of transparency is 10 critical to a company as we prepare for potential 11 approvals and potential launches. 12 Identifying and raising review issues and 13 concerns at these meetings and avoiding new issues 14 coming up late in the review process, particularly 15 after the late-cycle meeting, is key to review success. 16 Substantive review issues or significant 17 labeling challenges brought up late in the review 18 cycle, close to the action dates tend to defeat the 19 purpose of the mid-cycle and late-cycle meetings and do 20 make it challenging for both sponsors and the FDA to 21 ensure effective and efficient reviews. From our 22 experience, this should be an area of ongoing focus for</p>

<p style="text-align: right;">Page 78</p> <p>1 both sponsors and the agency.</p> <p>2 As I stated previously, the proposed PDUFA VI</p> <p>3 commitment letter builds upon the successes of the</p> <p>4 program and makes permanent the key components of the</p> <p>5 program, allowing sponsors and the FDA to benefit from</p> <p>6 the process improvements indefinitely.</p> <p>7 The goal of the program continues to be to</p> <p>8 promote the safe and effective development of new</p> <p>9 medicines and delivery of those in a timely manner to</p> <p>10 patients in need.</p> <p>11 FDA has been asked under PDUFA VI to update</p> <p>12 the Good Review Management practices guidances, and</p> <p>13 this is an opportunity for FDA to address other noted</p> <p>14 and important areas of review such as enhanced</p> <p>15 communications regarding the type and rationale for</p> <p>16 post-marketing commitments and post-marketing</p> <p>17 requirements.</p> <p>18 In conclusion, I would like to thank the</p> <p>19 agency for your efforts to meet the program's goals as</p> <p>20 outlined in PDUFA V. I believe the agency has not only</p> <p>21 met those goals but in many ways have exceeded those</p> <p>22 goals. We look forward to continuing elements of the</p>	<p style="text-align: right;">Page 80</p> <p>1 interactions with the agencies via phone and other</p> <p>2 means.</p> <p>3 For example, for one particular breakthrough</p> <p>4 therapy designated product, we had multiple</p> <p>5 collaborative meetings with the FDA that helped us to</p> <p>6 incorporate FDA's request in the dossier and resulted</p> <p>7 in rapid BLA review timelines and early approval.</p> <p>8 Having combined BLAs with two different</p> <p>9 indications under one review division was also very</p> <p>10 efficient. FDA worked with us to accept late data in</p> <p>11 an efficient manner, focusing on what was important in</p> <p>12 the process.</p> <p>13 In terms of best practices and learnings, I</p> <p>14 could share that maintaining early and open channels of</p> <p>15 communication is critical to the success of the review</p> <p>16 process.</p> <p>17 Insight into FDA's thinking on evolving</p> <p>18 strategy and review can really help industry understand</p> <p>19 information request from the FDA upfront rather than by</p> <p>20 follow-up conversations.</p> <p>21 Starting an early dialogue with both review</p> <p>22 divisions and CDRH for products with the diagnostic is</p>
<p style="text-align: right;">Page 79</p> <p>1 program under PDUFA VI. Thank you.</p> <p>2 DR. KHAN: Hello. I'm Tahira Khan, an</p> <p>3 associate program director at Genentech. I'm also in</p> <p>4 regulatory affairs. I also work in the policy office</p> <p>5 here in Washington, DC.</p> <p>6 I'd like to thank you for having me here and</p> <p>7 share Genentech's experiences with the PDUFA V program.</p> <p>8 Overall, our experience with the program has</p> <p>9 been very positive. The program clearly improved</p> <p>10 review efficiencies and has helped create greater</p> <p>11 transparency and open communication between industry</p> <p>12 and the FDA.</p> <p>13 We had a number of breakthrough therapy</p> <p>14 designated products that went through review cycle</p> <p>15 under this program. This review pathway has also</p> <p>16 worked really well for Genentech.</p> <p>17 FDA was readily available to talk to the</p> <p>18 product teams and shared their evolving thinking around</p> <p>19 complex issues throughout the review which was very</p> <p>20 well-appreciated by the teams.</p> <p>21 The additional face-to-face meetings under the</p> <p>22 breakthrough therapy review pathway helped later</p>	<p style="text-align: right;">Page 81</p> <p>1 also very important.</p> <p>2 Proactively providing the FDA methodology for</p> <p>3 analyses conducted and new label information was also</p> <p>4 essential, and it helped decrease the back and forth</p> <p>5 communication.</p> <p>6 From our end, frontloading of task such as</p> <p>7 labeled text (ph) was very helpful with the speed of</p> <p>8 the review.</p> <p>9 For breakthrough therapy designated products,</p> <p>10 requests for information can be issued very quickly</p> <p>11 after submission of NDA, and it is very important for</p> <p>12 the sponsor to develop a process for responding to</p> <p>13 these requests early and align with filing team</p> <p>14 members.</p> <p>15 It is also important to ensure that all</p> <p>16 manufacturing sites are listed by the industry as</p> <p>17 inclusion of new manufacturing sites could prompt</p> <p>18 inspection which could prolong assessment.</p> <p>19 We do recognize that it is also essential for</p> <p>20 quality requirements to keep base with clinical and</p> <p>21 nonclinical development programs for fast track</p> <p>22 products to shorten timeline to approval.</p>

<p style="text-align: right;">Page 82</p> <p>1 Label negotiations can go very fast with 2 multiple interactions even in one day. Therefore, it 3 is essential to have clear processes and structure in 4 place. 5 In terms of improvements, the evolving 6 landscape and thinking did lead to some inefficiencies 7 and unpredictability which however we think is 8 understandable. 9 It would be helpful for the sponsor to know 10 certain submission requirements ahead of time, such as 11 request for financial disclosure forms and summaries. 12 Information requests from the agencies are sometimes 13 difficult to provide and can take time on the sponsor 14 side. 15 Once responses are submitted, it would be good 16 to get some follow-up feedback from the agency on the 17 responses submitted and whether they were informative 18 or not. In certain instances, it may also be helpful 19 if we had requested teleconferences to clarify certain 20 FDA information requests. 21 The agency requested certain safety analyses 22 based on data points that were not prospectively</p>	<p style="text-align: right;">Page 84</p> <p>1 session. 2 Do we have any other questions? 3 (No response.) 4 No. Okay. So we are really ahead of 5 schedule. That concludes this meeting. Thank you to 6 everyone who came out today. 7 As a reminder, the public docket is open until 8 next Monday, April 3rd. You can submit any comments 9 over there. 10 If you are a non-FDA attendee, I'm just going 11 to ask if you can stay behind so we can escort you out 12 of this building. Thank you very much. 13 (Whereupon, at 12:45 p.m., the meeting was 14 adjourned.) 15 16 17 18 19 20 21 22</p>
<p style="text-align: right;">Page 83</p> <p>1 collected in the studies, and this was for certain 2 products, but they did not provide detailed guidance on 3 methodology. 4 Although we had provided our methodology in 5 the pre-BLA pre-meeting package, but we did not receive 6 feedback. So it would be helpful for us to get this 7 feedback early. 8 During the last stage of the review, it would 9 also be helpful if the agency could provide information 10 on what their target date is for signing the approval 11 letter. 12 Overall, we've been very pleased with the 13 efficiencies that we observed at the review timelines 14 and processes. We hope to continue to build on our 15 interaction and communications with the agency. 16 We thank the agency for it. 17 MS. HAFIZ: Thank you. If you want, you can 18 just stay there. That's fine. 19 We're now moving into our open public comment 20 session. I'm going to check with my colleague, Yoni 21 (ph), to see -- okay. It looks like we don't have 22 anyone who signed up for the open public comment</p>	<p style="text-align: right;">Page 85</p> <p>1 CERTIFICATE OF NOTARY PUBLIC 2 I, MICHAEL FARKAS, the officer before whom the 3 foregoing proceeding was taken, do hereby certify that 4 the proceedings were recorded by me and thereafter 5 reduced to typewriting under my direction; that said 6 proceedings are a true and accurate record to the best 7 of my knowledge, skills, and ability; that I am neither 8 counsel for, related to, nor employed by any of the 9 parties to the action in which this was taken; and, 10 further, that I am not a relative or employee of any 11 counsel or attorney employed by the parties hereto, nor 12 financially or otherwise interested in the outcome of 13 this action. 14 15 16  17 MICHAEL FARKAS 18 Notary Public in and for the 19 District of Columbia 20 21 22</p>

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12 April 6, 2017

13 DATE CINDY MCALLISTER

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