FOOD AND DRUG ADMINISTRATION

New Drugs Regulatory Program Modernization

Implementation of the Integrated Assessment of Marketing Applications and Integrated Review Documentation

Virtual Public Workshop

Friday, October 30, 2020

9:00 a.m. to 2:55 p.m.

Meeting Roster

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Joseph S. Ross, MD, MHS

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Meeting Roster (continued)

Lisa Skarupa, MSN

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Therri Usher, PhD

Richard White, NORD

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Welcome and Introduction

DR. STEIN: Well, good morning. I want to welcome everybody to this workshop on the Implementation of the Integrated Assessment for Marketing Applications. I appreciate everyone taking the time to join us in what I hope will be a very interesting, informative, and helpful session. I know we have several panels that I think will discuss this in detail, and I'm sure we'll learn a great deal and be able to take back as we continue to work on this process.

Just to give you a quick overview of the day, we'll start with some background information that I'll think you'll find useful in putting this integrated assessment process into some context. I'll just talk briefly about the modernization program for the Office of New Drugs and the New Drug Regulatory Program. We'll talk a little bit more in detail about the design features and the rationale for this new integrated assessment

process, as well as some of the external feedback we've already gotten and expect to get more of today.

We have then a break followed by a panel. We'll get input from external stakeholders and then have some open public comments from stakeholders as well, break for lunch, and then come back with a panel from the FDA perspective, folks who've used this new process, folks who've been involved in the design of the new process, and hear from their experiences and thinking on this, and then we'll wrap it up.

So again, I appreciate your coming to this and calling into this session, which I'm sure will be very useful for us and I'm sure very informative.

With that, what I'd like then to do is really to introduce the first part of our program. What I'm going to do is over the next few minutes talk a little bit about the modernization process in broader strokes. The integrated assessment is part of that modernization process, so I think it's

worth putting that in the context of what we've been working on to try to improve the way that we review and manage and regulate drugs within the Office of New Drugs and within the other disciplines that are involved in the new drug regulation.

To start with, it's important, as I said, I think to put the integrated assessment process into the context of the broader efforts that we're working within the New Drug Regulatory Program. When I say the New Drug Regulatory Program, I'm talking about efforts that go beyond just the Office of New Drugs, but also include our collaborating disciplines in the Office of Translational Sciences, the Office of Product Quality, and the Office of Surveillance and Epidemiology, all of which are involved with and work with us in the regulation of new drugs.

The vision of our modernization is to advance our leadership in the science and regulation of new drugs. Very simply, the mission of the Office of New Drugs is to maintain and

advance our global leadership in ensuring that the safe and effective drugs and biologics are available to the American people.

The strategic objectives of a modernization really come out of our vision and our mission, and I'll talk about these in more detail. They include scientific leadership, integrated assessment of our review processes; focus on benefit-risk monitoring throughout the lifecycle of the drug; managing talent, which is really what we work on, and it's the people within our organization that have the expertise, and the drive, and the dedication to mission that make all of this work; operational excellence, being efficient; and knowledge management, being able to leverage our experience to apply to what we're working on currently.

We've had a number of workstreams ongoing. They're at different stages. You may know that we organized the Office of New Drugs, a reorganization and restructuring that was completed back this year in March.

Just as we've all gone out to work

virtually, our reorganization and our restructuring was complete. We went from 6 offices to 8 clinical offices. We added infrastructure offices such as the Office of New Drug Policy, and we increased the number of divisions and made them more focused specifically on diseases with the offices that were more therapeutically aligned.

We've had other workstreams such as this integrated assessment of marketing applications, which is a workstream that's been going on now for several years in its design and now in the implementation phase of it as it's rolling out across the Office of New Drugs; a workstream on postmarket safety; an IND review management workstream; and an assessing talent workstream, again with the emphasis that the most important part of what we do is assuring that we are able to retain and help develop those really talented individuals we have within the Office of New Drugs and within our other disciplines within CDER, and that we then also can attract and develop new talent that is important to our mission.

There are a number of other workstreams that we're continuing to develop and work on. These are some of the examples of workstreams that are part of the New Drug Regulatory Program Modernization.

I want to say a few words about our thinking and the background, and the rationale for some of these changes. We know that the drug landscape, both for development and regulation, is changing. We've seen over the last year a sustained increase in the volume of drug development activity with rising numbers of INDs and an increased request from industry for meetings to discuss with us their drug development programs.

We certainly have seen increasingly complex innovative therapies under development with new platforms, as well as complex development programs using new methodologies and new approaches to clinical trials. We've seen certainly a greater availability of both observational and other forms of real-world data proposed to support new drug development and a different role for patients and public engagement. We've had a patient-focused

drug development process for some time now because we've recognized the importance of the patient's voice in helping us to understand the importance of the therapies and, really, how they should be developed and what endpoints are relevant.

We of course are all facing a relatively constrained ability to expand our financial base, so we have to be sure that we're efficient in what we do and the processes that we're utilizing. And of course we have tremendous talent within the Office of New Drugs and within CDER, but we have to be able to aggressively develop those people who we have here, providing them experiences that can help their career, but also attracting new talent as well. We needed to assure that we could simplify our processes and enable them so that we could give our staff more time to work on the science and less time to being doing the time and processes.

We certainly needed to make sure we have deep subject matter expertise. We have to evolve our regulatory policy to meet the changing landscape, so that's part of why we developed the

Office of New Drugs policy. We have new analytic techniques that we continue to work on and collaborate with external stakeholders in this, and make sure that as we restructured, we had a tighter structural alignment; as I said, disease-focused divisions and therapeutically aligned offices.

We also recognized how important a collaborative, interdisciplinary approach drug review was, which is really one of the underpinnings of the integrated assessment process.

We also recognized the importance of communicating our decisions in a clear and concise fashion, another clear underpinning for the integrated assessment process. We recognize that flexibility, certainly as we think about different data sources, was important, both in terms of how we provide advice with regard to new drug development programs but also postmarket surveillance activity.

Certainly, I come back again to the importance of both retaining and developing the amazing talent that we have within CDER and the

Office of New Drugs, but also attracting new talent into our organization to keep it vibrant and to keep our abilities to manage this program effective.

The strategic objectives really emerge from our mission and vision, and I'll go through these fairly briefly, but I want to emphasize that the integrated assessment really emerges from one of our key objectives for the New Drug Regulatory Program Modernization effort.

Scientific leadership, we want to make sure that we continue to develop our scientific expertise but that we also continue to contribute to and even lead changes in drug development and regulation that help it become more efficient and effective in identifying and developing and regulating and improving drugs that can be important for the health of the American public.

The integrated assessment process really was an objective to critically, collaboratively, and consistently assess information and submissions to determine if they meet our regulatory and statutory

framework, and benefit-risk monitoring throughout the lifecycle of the drug applied both increasingly effectively to how we review applications, but also in the post-approval environment.

I come back to managing talent, attracting, developing, and retaining outstanding staff. We have an outstanding staff already, but we need to make sure that their professional development is a focus of what we do and that we bring new talent into our organization, and operational exercise to standardize our processes so that we can be consistent, but also so that we can give more time to our staff to think about the clinical scientific issues and less time to process-related activities so that they can be doing what they're really good at doing, which is the science. Operational excellence, therefore, is really critical to delivering our staff to be able to be more efficient and effective and focus on the science.

Knowledge management, I can't say enough about the importance of understanding where we've been before, what we've seen before, and being able

to leverage that experience as we face new regulatory challenges and new issues. What have we done before in similar circumstances or in related circumstances? How can that inform our subsequent decisions? It not only helps the consistency of our decision making, but it's also critical in informing us and helping us think about each new challenge that we face from a regulatory perspective.

So with that background on the New Drug Regulatory Program Modernization effort, which the integrated assessment process is part, I think we can now dive into, in detail, the integrated assessment process, its development features, and its background rationale.

I'm going to turn to Kerry Jo Lee. Kerry Jo is currently our associate director for rare diseases in our core team, and our office that focuses on rare disease. But she also was a key member of the team that helped in the development of the integrated assessment. So she knows it inside and out, and I'll turn it over to Kerry Jo

to carry on and give us background on the integrated assessment process.

Kerry Jo, over to you.

DR. LEE: Thank you so much, Peter.

I am hoping everyone can hear and see me because I cannot see myself. Can someone confirm you can hear me?

DR. STEIN: We can hear you fine, Kerry Jo.

DR. LEE: Okay. Great. Thanks.

Presentation - Kerry Jo Lee

DR. LEE: Thanks so much for introducing me, and as Peter said, I'm Dr. Kerry Jo Lee, and I am one of the many contributors that the FDA has to the development of the integrated assessment. My purpose here today is really to both elaborate more on the background rationale, walk you through many of the core and design features of the integrated assessment, and hopefully answer some of the more common questions that we hear regarding the integrated assessment.

So how did we get here? Well essentially, several years ago, we had already heard from

external stakeholders that they desired clearer communication surrounding the decision making that we had over marketing applications here in CDER. We convened a regular internal group and cross-discipline reviewers that included regulatory experts and included people from all different levels, from division director to primary reviewers.

We wanted to work on trying to identify if there were elements of the marketing application review that we could improve upon, what would those be? Basically, what we heard was that people felt that discipline-specific reviews led to a lot of redundant work, resummarizing what other disciplines had already said, and that there was a strong desire for additional clarity on the rationale of the interdisciplinary review issues.

We heard from people that reviews centered by discipline rather than interdisciplinary collaboration on review issues could potentially be a problem because it really led to some difficulty in seeing the bigger picture and finding all of the

relevant concerns, and analyses, and assessments that were necessary to understand one key review issue when it was scattered over multiple different reviews.

We also heard from reviewers that they asked for support to spend time on critical thinking, which is what they were brought to the FDA to do, based on their scientific expertise, and wanted to spend less time on editing and formatting documents or other programming tasks. Then finally, we really saw that there was an opportunity, and Peter also underscored this, and a need for better knowledge management.

So in developing a new process and template, we had an opportunity to try and standardize and better find elements, and locate them in the review, key elements that we wanted to capture, as well as the ability to potentially build into the ability to extract that information from our reviews easier.

Out of this group came the beginning ideas of an integrated assessment process and template

for documentation that really supported each other, and this process and template centered around three core ideas, and one of them was the idea of communication. This is communication both internally to stakeholders and collaborators who are writing collectively on issues, as well as to external stakeholders for our regulatory decision making and rationales.

The second color was interdisciplinary. So again, in terms of both collaborating on these issues and not being as redundant, we really wanted to promote the interdisciplinary aspect of marketing application review, which we all came together to provide our perspective on.

Then thirdly, issue based. We really wanted to hone in on what were the key issues that contributed to our decisions and ensure that those were really well characterized and people could easily understand the thought, effort, and decision making that went into each of those key issues. Key issues in general I will say are comprised of issues that informed or characterized our

assessment of benefit and risk.

After defining the core elements, when we started this process, we really realized that we had several goals. One of them was that we really wanted this to be team-based and that we wanted to continue our standard of scientifically rigorous reviews, but we wanted to enhance that process with very strong interdisciplinary collaboration.

We wanted this to be efficient, issue-focused assessment that was supported by new roles. We also wanted to enhance communication within the review team and with our external stakeholders. We primarily also wanted to clearly articulate the basis for regulatory decisions. And finally, we wanted to increase our support for review teams that were adapting to this new process.

So not only did this include supporting roles of clinical data scientists or medical editors, which I'll further define later, but we also have developed a really robust suite of on-demand resources, training, ambassadors, and

peer support, as well as seamless workflow management to support this process.

This led to the core components of the integrated assessment. So really at its core, the idea of an integrated assessment is a new process, and this new process is very focused on early identification of review issues, to the extent possible, and interdisciplinary collaboration. So this gives reviewers a lot of time to really identify and spend their time working through the core review issues of a marketing application.

We wanted to have a new template that enabled issue-based and interdisciplinary review documentation, and then we also wanted to have some new roles such as a clinical data scientist and a medical editor to really take that burden off of reviewers and enable them more time to focus on these key issues for critical thinking.

Taking a closer look at the integrated assessment document, it's a three-part document, and it's made up of the executive summary, the interdisciplinary assessment, and appendices. I'll

go into the elements of those in a few slides. The recommended lead authors for each section are listed here as well.

The executive summary is really your highest level overview, so you have the signatory authority, the cross disciplinary team lead, the clinical reviewer, and the OND division director contributing to that section. You have the clinical; clinical pharmacology; all of the core review disciplines; clinical microbiology; pharm-tox; statistical and virology reviewers; and any other subject matter experts that need to contribute to the core elements of the review writing and interdisciplinary assessment.

In the appendices, you have your regulatory project manager for regulatory history, additional data and analyses provided from each of the core review disciplines, and labeling information there as well, as well as other subject matter experts.

To go further into depth of what is contained in each section of the integrated assessment, key features of the executive summary

are provided here. You have a brief summary of the regulatory action. You have an overall agency assessment and an overview of the major decisions and rationale. You additionally have included, the benefit-risk framework and assessment. This has been found in all our reviews for some time. It will continue to be there where you can see the summary of the major benefits and risks, how they were assessed, and how they were weighed against each other.

The second section of the template is the interdisciplinary assessment. I really want to underscore a bit, this is, really, the critical and important core data regarding efficacy, safety, clinical pharmacology, and pharmacotoxicology. You'll see the frame and the program overview, but it also includes detailed interdisciplinary discussion of key safety and efficacy issues critical to the regulatory decision; so it will also include integrated focused assessment that highlights key issues the review team thinks are pertinent to the decision-making process.

This is key features of the appendices. This serves as a repository of materials that support or are vital to the summary document and conclusions in the interdisciplinary assessment. It will include all supporting reviews for the application, so anything a subject matter expert may have provided, the regulatory history, the labeling summaries, as well as division-specific sections that contain all additional analyses.

There is an addendum for work done that may have directly impacted the decision-making process, but you really wanted to capture as a reference for future work that's important either to external or internal stakeholders.

We are a scientific organization. People come and work here after training many years, gaining their scientific expertise and perspective, and that's what we want them to bring to the review of marketing applications, therefore, we expect that there may be times when these perspectives differ. So I wanted to make a few points clear about the integrated assessment.

The first is that the integrated assessment, both the process and the documentation, embrace and respect scientific differences of viewpoints. The second is that the process allows for the capture of an opportunity for early, frequent, and intensive meetings around any differences of opinion that may arise. The third is that meaningful differences on important aspects of the review or key review issues, even if they are resolved, should be described in the discussion of key review issues or in other appropriate parts of the integrated review document.

The fourth is that differences of opinion that remain at the time of the marketing application decision can be documented as a full review of the issue in a separate write-up, and that would go with all additional reviews that reside in our appendices. I'm going to spend the next few slides really walking through and trying to illustrate what this might look like.

We have several avenues for expression of scientific disagreement and equal voice. The first

is in the process itself. We have many more issue-focused interdisciplinary meetings allowed for in this process. This is a forum for frequent and thorough discussions of key issues, particularly since we're focusing so much on the early identification of potential issues. At these meetings, we fully expect that people will be sharing, addressing, and discussing their differences and viewpoints.

In terms of documentation, there are multiple avenues of documentation in which these will be described. The first is in the executive summary. This should include a high level description of any key scientific differences of opinion and the final decision by the signatory authority. It will summarize any major differences of opinion and documentation for each reviewer or discipline and the rationale for the resultant regulatory action.

In the second part of the template, the interdisciplinary assessment, this is where we would include discussion of differences in opinion

that regard the key review issues on the review team and how scientific disagreement was addressed, and I'll show you a little further illustration of what that might look like later.

In the appendices, you'll see separate reviews written by reviewers who may disagree with significant elements of the executive summary and the interdisciplinary assessment sections or the marketing application decision of a signatory authority. Just as they always have for approvals, all elements that are non-proprietary and not redacted of these reviews will be made public. So the executive summary, interdisciplinary, and appendices would all be public documents.

Just to further walk you through what this might look like, review issues in general are sketched out according to common parameters. First, you'd have to describe the issue; second, you provide the background analyses; third is your assessment; and fourth is your conclusion. So if you had disagreement between two different review teams, in the conclusion, you would run the data

interpretation or assessment and action taken. You would find the clinical review team -- and these are just illustrations here -- perspective and the conclusion, the team that might differ from them; say it's the nonclinical review team perspective, and then conclusion.

Thirdly, you would have the signatory's perspective, which identifies which perspective the signatory, he or she, aligns with and why. I would also like to call out that if a difference of opinion is related to a very significant element of the planned action -- so labeling, postmarketing actions, or the overall decision on the marketing -- this is where we would fully expect an additional separate detailed review that would accompany the review document in the appendices.

Before I go on, I would just say that on scientific differences of opinion, we actually expect that this in many ways will make it clearer as to where we've disagreed, what the rationale was, and what final action was taken.

Here, I just want to talk a little bit more

about the new roles that we've incorporated, and those would be those of the medical editor. This person, generally, is really there for support in formatting and editing the integrated review documents. Reviewers can focus on critical thinking.

The clinical data scientist is going to provide key safety tables and figures needed early in the review and in collaboration, close collaboration, with clinical reviewers for them to provide their expertise, really, in the elements of the disease, the manifestations that you might expect, the elements that you might expect regarded to drug class, and their expertise in the indication. Together, they execute a safety data analysis plan to improve the efficiency and quality of the clinical review.

Thirdly, we have the enhanced clinical and regulatory partnership. Because the process and document are really so part and partial surrounding the focus on key review issues, the clinic cross-discipline team lead and the regulatory

project managers really need to work together utilizing the respective expertise to identify these issues and focus the meeting around these issues to lead the interdisciplinary review process.

Given all of this, what are the implications of us implementing this interdisciplinary review, focusing on these key review issues? Well, we're really hoping to achieve all of these things. One would be increased readability. Readers, both internal and external, we're hoping can really pull a picture together better and quickly identify what the critical issues were that weighed into our decision making, as well as the rationale surrounding those. There's also the improved clarity surrounding our thinking and decision making, and finally, further transparency into the rationale for regulatory decision making.

So putting all of these things together, we're really hoping to achieve enhanced insight, utility, and knowledge management of all of our marketing application reviews.

I talked a lot about key review issues, but what might these actually look like? Examples of issues related to benefit would be the acceptability of the primary efficacy endpoint; failure of one of multiple trials; failure of one component of a composite or co-primary endpoint; concerns regarding optimal dosing; evidence of the contribution of components for a fixed-dose or combination product; or subpopulation factors affecting benefit.

Examples of issues related to risk might be those that are significant or serious adverse events related to the administration of the drug; trial design that impacted the reviewer's assessment of causality, so controlled trials or no placebo; significant or serious adverse events related to the drug class, so those related to serious things like hypersensitivity; subpopulation factors affecting risk; nonclinical data that might have shown a significant or a serious signal that remains a concern but were not seen during the duration of a clinical trial; and considerations

for the drug mechanism of action that might lead to a safety issue.

In my final few slides, I want to address just a few other issues, and one of them is related to the different types of reviews out there. We have several. So what people are most familiar with are likely either our traditional reviews, which we've talked about. Those were, separate review disciplines have separate review documents that are authored independently by each discipline.

You also, several years back, may have seen another one of our multidisciplinary reviews, and that is what we referred to as the Unireview. This was where disciplines all contributed to one review, but they all had their complete distinct sections without an integrated approach to key review issues.

If you had a key review issue, even though all the reviews were in one document, you still might have seen one discipline refer to it on one page, another discipline refer to it from their perspective on another page, and another one,

hundreds of page later, weigh in on their perspective. So although all the disciplines were contributing to the review, they were not all collectively working together to write about key review issues.

The challenges with both of these types of reviews, whereas as you saw here, these were discipline-specific reviews, rather than issue-focused, you really saw discipline-focused reviews. So there was a lot of parallel and redundant work and writing, and this essentially translated into obscuring the rationale for our decisions to any stakeholders reading our reviews.

Therefore, these have evolved into our next iteration of the review, which is the integrated assessment, which we really look at as being an integrated, cohesive, issue-focused document that retains discipline-specific detailed information. I want to focus that it definitely does retain that discipline-specific detailed information; you just have the benefit of seeing integrated and cohesive writing around the issues that touch upon multiple

disciplines.

Overall objectives of this were to develop an integrated interdisciplinary approach, as you've heard several times today, to address key review issues; reduce redundancy; and improve clarity on our rationale for regulatory decision making.

I would also just like to point out, you may have also heard about other types of reviews, and one of those would be the summary level review. That is not what the integrated assessment is either. That really relies on qualified data summaries to support the approval of supplemental applications for a qualified drug use. So that is very distinct as well from the integrated assessment.

Here, I would really just like to point out to help people where they would find certain types of information. If you were looking for nonclinical safety assessments, you would find a summary of it in the risk and risk management section of the interdisciplinary assessment, and you might find more detailed reviews of studies in

their own dedicated appendix.

For clinical pharmacology assessments, you would find a summary of key pharmacokinetics, clinical pharmacology data, and activity that is really critical to understanding the marketing application in the interdisciplinary assessment, but you might find detailed review of clinical pharmacology studies in a dedicated appendix.

For the effectiveness assessment, you would find an overview of the trial; trial design critique, analysis of the endpoints, the results, and interpretation; and statistical efficacy assessments and its relationship to clinical benefit in the interdisciplinary assessment. However, you would then find perhaps additional trial design critiques and statistical subgroup analyses that might not have been directly related to the decision surrounding substantial evidence of efficacy or review issue in the appendix.

Safety assessment. In the interdisciplinary assessment, you would see the overall approach to

safety review, safety database adequacy assessment, key safety findings and concerns, and risks and their characterization, including any postmarketing actions that were taken in the interdisciplinary assessment. You might find more detailed subject level information or data analyses or modeling supporting these key safety findings in the appendix. Then finally, just to reiterate, the benefit-risk framework and assessment will remain, and it will be incorporated in the executive summary for support into the overall decision making on the application.

That is the end of my presentation. I really hope that this has been a comprehensive overview that provides some information and context to set the stage for all of our discussions later on today. At this point, I'd like to turn it over to my colleague.

Nancy Sager is the director of the Division for Information Disclosure Policy, and I'm hoping that Nancy can help to provide even more clarity on the distinctions between the integrated assessment,

which is a review of the marketing application and the overall action package. So thank you for your time.

MS. SAGER: Thank you, Kerry Jo. I'm hoping people can hear me, and if the support staff can hear me, I'm getting an error message that I can't start my video because the host has stopped it. Okay. Now I can start it. Thank you.

Presentation - Nancy Sager

MS. SAGER: I'm going to provide a brief overview of action packages and how they fit into the drug approval process. It's important to note that in 2018, we streamlined the information that we included in the action package. This effort was independent from and done before the integrated assessment pilot started. We know that action packages are the critical information that goes to the outside world. Once the reviewers finish their assessment and approve an application, this is how we communicate our decisions, communicate our reasons for the decision.

Action packages have been around since at

least the 1990s. The original purpose of an action package was to provide a consolidated set of paper documents that the deciding official could reference when they were deciding to approve an application. The original content of an action packages, as pulled together by a review division, was not designed as an outward communication tool.

We started using the action packages in approximately 2001. We had gotten many requests from the public for information around original NDAs and, subsequently, original BLAs whence we took over the review responsibility for therapeutic biologics. They didn't want to have to submit Freedom of Information Act requests for this approval information, so we started what we call a Proactive Disclosure Program to post the approval information on Drugs@FDA without the public needing to submit a Freedom of Information Act request.

Now, this was limited to, as I say, original NDAs and original BLAs. Another kind of milestone in action package history is that in 2007, the Food, Drug, and Cosmetic Act was amended to require

the posting of certain action packages. So we were voluntarily doing it, and Congress added some requirements regarding the publication of action packages in the statute. It also defines the contents of an action package. A cross-discipline team CDER and CBER was involved in implementing this provision. We kept using the same action package that had always been prepared mostly for internal use as our communication tool, relating to approvals of drugs.

Then in 2018, based on projected workload, CDER identified the need to evaluate and streamline the content of the action package. It wasn't connected to the integrated assessment development program, but it just happened to coincide at the same time.

The number of NMEs was skyrocketing. We wanted to be able to disclose the information in a timely manner, but the action packages were getting larger and larger and larger and filled with some information that we didn't feel was -- to provide for our approval decision. So the disclosure staff

worked with OND to identify the most scientifically meaningful information and other content required by the statute, and we've prioritized this and posted it in a timely manner.

In a current action package, what is included? All the discipline and multidiscipline reviews are included; the multidiscipline reviews by whatever name they go by and the integrated assessment if there is one. Consult reviews, when we consult with another center like CDRH, are included. Action letters, so approval, tentative approval, complete response, and refuse to file letters would be included in an action package. If there's a formal dispute resolution request pertaining to the approval action, those correspondence would be included.

Meeting minutes related to the format and content of the application such as pre-NDA and BLA meeting minutes and end of phase 2 meeting minutes are included. The approved labels and REMS are also included, and any kind of summary review from the deciding official, division director or office

director -- because it takes different formats depending on the type of review that's being done -- that's included. An officer and employee list is also included.

What is not included in an action package now that could have been included in past action packages? Any checklist driven review. There was a project manager physician labeling rule checklist that was always completed; filing reviews; things more ministerial in nature; information requests and other emails; and letters other than the action letters that are included.

Consult requests used to be included, and they're not included in action packages anymore; other types of meeting minutes; draft labeling, which was always important when an action package was used by a deciding official. It's not important for disclosure, for communicating to the outside world, because we always withhold draft labeling as confidential commercial information. So that's now not included in the action package that's provided to us from the review division.

Telephone consults, debarment and patent certifications, and any kind of other checklists or templates that are more ministerial in nature are excluded.

What are the options for information that isn't proactively posted? We only proactively post the original NDAs and BLA action package information, but other types of approval information like chemistry supplements or ANDA applications are requested under FOIA and satisfied in that manner. If it's approval-related information, once we process the request under FOIA, we do post it on Drugs@FDA if somebody asks for the review information for actions that we normally don't proactively post on drugs at FDA.

Also, if there's additional information about any particular approval action, you can always submit a FOIA request asking for additional information, if it's information that's outside the scope of the action package, information that we commonly post. I also want to say that the content of an action package evolves over time because new

types of reviews are created, or there are new statutory requirements that require us to now look at something that we've never looked at, and it may be a new type of review. We're constantly adjusting what's in the action package, based on what's happening in the review process.

So with that, I'm going to turn it over to Rhonda Hearns-Stewart, who is the associate director of implementation, who will now talk about the implementation of the integrated assessment.

Presentation - Rhonda Hearns-Stewart

DR. HEARNS-STEWART: Thank you, Nancy, and good morning.

Our vision for implementation of the integrated assessment of marketing applications is to, over time, use the integrated review for all new drug marketing applications, including supplements in the near future, and to continue implementation in a phased manner that enables an iterative approach through evaluation, feedback, and refinement to the process and template as necessary after each phase of implementation, and

to also support successful transition of review teams by providing ample tools, training, and resources.

We are currently in phase 6 of a 7-phase implementation for new molecular entities, original biologic licensing applications, and select efficacy supplements such as those with new indications or a new population. This first round of implementation is to introduce divisions within CDER's Office of New Drugs to the new integrated assessment, the process, and the template.

All phases are currently ongoing with the expectation that each division will use the new integrated assessment for at least one marketing application. As I mentioned, with all of these phases currently still being ongoing, they will continue as we continue to introduce additional divisions and reviews to the new process, templates, and training tools.

The vertical light blue lines that you see here on this figure represent scheduled periods of evaluation. These evaluation periods consist of

feedback synthesis with subsequent refinement of the process, the templates, and/or training as necessary. In addition to receiving feedback from our review teams, senior leaders within the agency are also evaluating completed integrated review documents. To date, there are 12 completed integrated review documents and there are currently 21 ongoing marketing applications for which the new integrated review template is being used.

To help our review team successfully transition to this new process and the new template, we developed several resources, including live and self-paced trainings, now virtual; peer ambassadors who are discipline-specific colleagues who have used the integrated review template and gone through the process.

Ongoing support is provided by coaching of our review team. We've developed a number of quick start guides for topics that include but aren't limited to effective collaboration and best meeting practices. We've also developed a review issue list to help our reviewers capture review issues

specific to the marketing applications. We have how-to guides specifically for the process and another specifically for the template. We've developed a list of frequently asked questions with answers to be used as a resource for our reviewers.

As I mentioned, we do have this phased implementation, which includes the opportunity for feedback evaluation, and that feedback and evaluation results in refinement to the process and the template, as well as the training tools. Key feedback sources include surveys; focus groups; interviews; an anonymous feedback portal with repository; public comments; Federal Registry; meeting observations; and division orientations, comments, and questions that we receive from them, division orientations and also other presentations within the agency, we have developed a repository for those as well.

Key feedback sources generate a diverse range of helpful feedback. We've learned that our reviewers do require additional learning and guidance to understand how to most effectively

collaborate. We've also learned that the new roles of the clinical data scientists and the medical editors have helped drive efficiency during this new process. We've learned that the new process and template do allow critical thinking and collaboration, and this issue-based review format does decrease redundancy in writing.

This slide demonstrates how we have addressed some of the critical feedback that we've received from our review teams. Our review teams requested additional guidance on collaboration and how to write collaboratively.

This is a quote from an RPM. "More guidance or more specifics on working together would be helpful." Therefore, we developed an effective collaboration course. We are also on target to launch a co-leadership course specifically for our team leaders and our regulatory project managers as they work together to co-lead this new process.

Review teams also requested guidance on how to write and also how to review the co-authored sections of this integrated review document,

specifically on the deadlines that may need to be set in order to accomplish this task. One clinical team lead wrote, "Courses did not address the order in which reviewers should write or review the document for sections that were written by more than one author." Therefore, we developed writing milestones for these teams, and we've incorporated the writing milestones into all of the appropriate courses and training resources as appropriate.

We've also heard positive feedback from our review teams. We have categorized this positive feedback, some of the positive feedback, into three categories. These next three slides will review those three themes for you, the first theme being that the new roles of clinical data scientists and medical editors create efficiency.

Ninety-one of our reviewers surveyed agreed that the medical editor was helpful, especially with formatting and editing the review. Leadership agreed that the huge undertaking for updating the tables and ensuring that the hyperlinks are working within the document was very helpful to the review

process.

A clinical primary reviewer indicated that the medical editors helped save time so that they could focus on content of the review, and 80 percent of clinical primary reviewers agreed that the clinical data scientist is very helpful with conducting analyses. This is a quote from a clinical primary reviewer. "The clinical data scientist is an expert in statistical software and has been incredibly helpful in generating standard tables and additional analyses."

We'll move to the second theme, which is the process and template to foster critical thinking and collaboration. Seventy-two percent of reviewers surveyed agreed that the new process enabled effective interdisciplinary collaboration.

This is my favorite quote. It's from a biostats primary reviewer. "I've been around for many years, and this is the most interaction I've had with clinical, and the most creative and critical thinking I've done."

A division director also agreed that this

new process support integration and is a great improvement. Eighty-three percent of surveyed reviewers agreed that they have the time they need to critically think through high-impact issues and their regulatory implications. From a clinical primary reviewer, "The new issue-based approach encourages thinking about how your analyses tie into the bigger picture."

The third theme and final theme that I will go through is that writing a single integrated review decreases redundancy. I have a few quotes from various disciplines here. An RPM indicates that, "When you actually write in the shared template, it helps other disciplines avoid doing the same work," "Less redundancy" from a pharm-tox reviewer, and from an office director, "The overall process is an improvement, and you do not have replications and redundancies of disciplines."

Five out of six office or division directors surveyed agreed that the integrated review was structured around issues and included only relevant information. Five out of six office or division

directors surveyed also agreed that important information was not missing in the final work product. The sixth director surveyed was neutral.

I will close by just stressing the fact that this is an ongoing implementation. We will continue to collect our feedback from our review teams and modify the process template and training tools as necessary. Thank you for your time and attention. I will now turn it over to my colleague Yoni Tyberg, the acting team lead for the special program.

Presentation - Yoni Tyberg

MR. TYBERG: Again, my name is Yoni Tyberg. I'm the acting team leader for the special programs staff within OND, and our office oversees and supports the implementation of the New Drugs Regulatory Program Modernization effort, which as Dr. Stein opened up on, contains many workstreams. With the implementation of many of those workstreams, our team also provides a program evaluation component across all of those workstreams to include the integrated assessment of

marketing applications.

As part of our evaluation approach, as Rhonda indicated in her session above, we requested input from you, the stakeholders, to hear and give opportunity to voice your perspectives, and we obviously take those very seriously. So my session today will be focused on the feedback that we've gotten thus far, a synthesis of that feedback, and some of the emerging themes that we've seen.

Back in 2019 when we were just beginning and when we were wrapping up the design of the implementation, we submitted to the FRN notice one review that we retrofitted into an integrated assessment review, and the following year, earlier this year, 2020, we've submitted two reviews in the Federal Register notice to solicit input from you all as the stakeholders.

The intent there was to, again, gather input on the integrated review documentation, and we were specifically interested in feedback across several key dimensions, one being the impact of the new integrated assessment format on the stakeholders'

understanding of the FDA's basis for making a regulatory decision; number 2, its usability and accessibility of information that's within the document; 3, recommendations for improvement to meet the needs of our stakeholders; and number 4, some advantages and disadvantages of the integrated review template.

In summary, both the 2019 notice, as well as the 2020 Federal Registry notice, and comments, we heard from a total of 15 respondents who submitted detailed letters. Those demographics of the respondents included an array of scientists; academics; industry; patient advocacy groups; and individuals.

I'll just stop for a moment and note that the 2020 FRN notice is still up and live now, and is accessible, and I believe available through December. We look forward and we encourage the stakeholders to continue to submit their comments so we can look at those and, again, act on those.

The summary of those comments, of those 15 respondents thus far, we divided into two buckets,

and we labeled them as some of the potential concerns and benefits. For those potential concerns, we've unpacked those into three separate domains: one being one voice, the potential of groupthink; potential loss of detailed data and information that could be potentially found in the document; and the potential loss of insight into the regulatory process.

For the benefits we noted, one is the document improves the clarity of the review document; the document itself improves the usability; and the last bucket we divided it into was the document itself drives a more holistic assessment by the reviewers, by the different disciplines.

In the next few slides, I'm going to just drill down a little bit into some of those themes, those descriptions, and some example quotes to help support. As noted in the bucket of some of those potential concerns, some respondents voiced concerns over these potential future reviews. For the theme of groupthink, what was described within

all the synthesis was this potential loss of individual review perspectives; insight into the reviewers' decision making; and the potential loss of the differences of opinions amongst the reviewers and disciplines.

We have a quote here, and I'll quote, "Eliminating the production of such review documents by the individual disciplines could lead to dangerous groupthink and inhibit the expression of important minority views." That was from one of our patient advocacy stakeholders.

The second theme of potential loss of detailed data and information, here we describe a potential loss of comprehensive information and data, and we've given some examples of both clinical and nonclinical trial design data, its data, and analysis.

Here, a quote that's helped support, "The comprehensive information and data contained within the FDA's action package are a valuable and unique source of data for assessing the efficacy and harm of drugs. The integrated review will result in a

loss of data on published and unpublished clinical trials." That was provided to us by one of our scientific stakeholders.

Finally, the potential loss of insight into the regulatory process, here we describe that theme as the potential loss of information due to lack of published documents related to FDA's decision-making rationale. Here the quote from one of our industry stakeholders is, "There's potential that the integrated reviews lack information regarding why a specific request has been made and why FDA found the response acceptable."

As we jump to the next slide, I want to demonstrate what FDA is doing, which has been voiced in the previous session by Rhonda, but I'll just voice those over and include those in some of these themes.

We here at FDA are actively addressing many of those concerns raised. For the first theme, for the potential for groupthink, FDA and our team have defined guidelines for documentation of scientific differences of opinion within the process and

template to provide clarity and avenues for discussion and documentation.

Again, as noted above, in the above sessions, we do this in two ways. One is, embedded now into our review process are these new meetings. We call them JAM sessions, and the acronym is joint assessment meetings. In these meetings, which are new to the process, it really encourages issue-based discussions related to the review and the review issues. So it enables that interconnectivity with many of the disciplines, which as noted also was lacking a bit. It's been noted as well that many of the reviewers have enjoyed that.

Secondly, once we've spoken out those issues and discussed those issues, how are we documenting them? As noted, we have an executive summary; review issues section; our appendices; and our discipline-specific sections within the IRT, which again allow for those reviewers to document areas where there is potential differences of opinion.

The second theme of potential loss of

detailed data and information, here each discipline is still required to provide a detailed assessment of data. Additional detailed information is available in the discipline-specific appendices, which include the supportive documents, assessments, and analyses, as well as documents, assessments, and analyses of import to key facts, data, or conclusions of the review.

Finally, regarding the theme of the potential issue of the loss of insight into the regulatory process, really, the intent behind the integrated review template, one, it provides a stand-alone regulatory history section that summarizes the regulatory history of the drug product and includes key regulatory decisions made throughout drug development, as well as underscoring and complementing; that is it provides insight and clarity into the regulatory process through an interdisciplinary lens.

Moving on to the benefits, many respondents did express benefits of the IRT. One here is the first theme of improving clarity of the review

document. The description there is it clearly delineates rationale for regulatory decisions; clearly outlines the benefit-risk assessment; and there is value found in the executive summary.

As an example, a quote here from one of our industry stakeholders, "Use of the IRT," or formalize the use, they're saying, of the integrated review documents, "as a comprehensive and more effective approach to providing clarity on FDA's decisions regarding regulatory approvals, but ensure that the combination of integrated review documents and its appendices is no less comprehensive in the existing documentation."

The second bucket of benefits we heard was improve the usability of the document, and here we describe that as being the new format is easy to navigate and the information is written in a way that should be accessible to a range of audiences. Here the quote, again, from another stakeholder, one of our stakeholders from the industry, is, "Usability and accessibility of the new integrated format is improved compared to the original review.

The new format begins with a succinct summary of the regulatory action and the basis of the action."

Finally, the second benefit, it drives a more holistic assessment by the reviewers and disciplines, and this new format is described as the new format provides a comprehensive summary of the input from reviewers from all relevant disciplines. Here from one of our patient advocacy stakeholders, "It is helpful to have a summary of review input from all disciplines in one consolidated document rather than separated as is in the approach in the current review document template."

As with every area of concern and area of benefit, we do want to make sure we track those benefits and continue seeing those benefits and change over time, and making sure those changes over time still retain those benefits. Here regarding the theme of improving the clarity, this is one note for the actions that were taken and what we've heard is that reviewers have also agreed that the integrated review document does provide

more clarity as they focus on key review issues. The FDA intends to continue soliciting and evaluating feedback from the public to evaluate clarity of these review documents.

In terms of our usability, Rhonda initially had indicated above one of our components of our evaluation is to solicit feedback from our senior FDA subject matter experts to continue evaluating, in those completed integrated reviews, those documents for usability, and likewise, as above, we again will continue to solicit evaluating feedback from the public.

Finally, the same applies, those two elements of our evaluation, to making sure that the benefits are retained for driving that more holistic assessment by our reviewers and disciplines, we again will intend to solicit both our senior FDA subject matter experts to continue to evaluate that piece, as well as, again, continue to solicit and evaluate feedback from you all. Again, I just want to remind you before we jump to break, the FRN notice is still up and running

through December, and we encourage and hope to hear more from our stakeholders at large.

That concludes the external feedback and synthesis session. It looks like we're running a little bit early. I do want to remind everyone that as some questions have been coming through our portal, through our chat, I just want to thank you for your questions. All questions will be gathered and reviewed, and if time permits, questions will be addressed during the workshop, so thank you.

We now will have a break scheduled at 10:15. We're running a little bit ahead of schedule, which is good, so we can extend our break to grab an extra snack or grab an extra coffee. Please remember to join back here with the panel. We're going to have our external stakeholder panel, which will begin promptly at 10:30. Thank you.

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

Panel Discussion

DR. CONNELLY: Hi, everyone. Welcome back from the break. My name is Sarah Connelly. I am

pleased to be joined with my co-moderator John Farley, and we just got the notification, John, that we can go ahead and start the session. So I'll turn it over to you to kick us off.

DR. FARLEY: Fantastic. Thanks, Sarah.

I'm John Farley, director of the Office of Infectious Diseases in New Drugs at FDA. We're very excited to facilitate the panel, focused on external stakeholders' perspectives and their impressions. This process really started several years ago, as has been shared, with FDA reaching out externally to stakeholders representing the same entities that are represented on this panel, focused on what they would like to see different about FDA's, particularly, review products, the template itself, and what becomes available after a drug approval.

So FDA took that advice and has developed both the process and the template that you're hearing about today and getting to see, so we're very keen to get their perspectives on what they think. So without further ado, why don't we go

ahead and get started.

Sarah, I think you're going to introduce all the speakers and get things moving.

DR. CONNELLY: That is right. As I said, my name is Sarah Connelly. I'm currently serving as an acting clinical team leader in the Division of Antivirals at FDA, and I've been involved in the integrated assessment process component of this and honored to be moderating the session with John. We'll have our panelists today each share their presentations or remarks, and then we'll have a panel Q&A. As you'll hear in my introductions, we are so incredibly fortunate to have such an esteemed panel who bring a wealth of really important perspectives on their impressions of using the integrated review template.

So it's my pleasure to first introduce Dr. Naga Chalasani, who is representing the American Association for the Study of Liver diseases. Dr. Chalasani currently serves as David W. Crabb Professor of Medicine and interim chair of the Department of Medicine at Indiana University

School of Medicine, and also served as the director of the Division of Gastroenterology and Hepatology.

In addition to his extensive number of publications, he's the lead author for the AASLD Practice Guideline on the Diagnosis and Management of Non-Alcoholic Fatty Liver Disease and lead author on the American College of Gastroenterology Practice Guideline on the Diagnosis and Management of Drug-Induced Liver Injury.

Welcome, Dr. Chalasani. Thank you so much for being with us today and sharing your perspectives regarding the integrated assessment of marketing applications on behalf of AASLD, and I'll turn it over to you.

DR. CHALASANI: Thank you, Dr. Connelly, and thank you, Dr. Farley, for the invitation. I'm pleased to be here today. My name is Naga Chalasani. I don't have slides to share. I'm just going to read my statement.

My name is Naga Chalasani. I'm a practicing hepatologist at Indiana University School of Medicine. As was mentioned by, Dr. Connelly, I'm a

clinical researcher focusing on non-alcoholic fatty liver disease and drug-induced liver. I'm speaking for the American Association for the Study of Liver Diseases today.

I want to thank the agency for inviting us to take part in this important workshop as one of the external stakeholders. First, I want to thank and congratulate the Office of New Drugs for completing its reorganization and for articulating its NDRP Modernization vision. A critical component of the modernization is the integrated assessment, which aims to critically, collaboratively, and consistently assess if an NDA submission needs legal and regulatory requirements and to better communicate the rationale for the decision taken.

As I read through the material and listened to the presentation earlier this morning, I believe integrated reviews are highly meritorious and are sufficiently distinct from the current process, which although can be interdisciplinary has been prone for redundancy and inconsistencies in the

process and quality. Initial feedback from public stakeholders on the agency's divisional leadership and medical reviewers is quite favorable. The agency's plans for phase-in and the timelines are well thought out.

As I listened through the agency's presentation this morning and read through some of the material available in the public domain, several thoughts came up in my mind, and I will state them here. First, identification of the key issues and establishing the collaborations is the critical first step. How iterative is this process and who is responsible for this step? How can one assure consistency across different individuals responsible for this critical step?

Second, it is not entirely clear to me how well the patient's perspective is included operationally in this process. Are they at the table when some of the discussions are undertaken? It's not clear to me.

Third, it is great that scientific disagreements are included in the integrated

reviews. How would one avoid someone taking these disagreements out of context?

Fourth, would such an integrated review offer rationale for critical elements contained within the package insert where it is applicable?

Five, talent acquisition, retention, and resources are critical for smooth phasing in of the NDRP Modernization and its sustenance.

Six, who are the medical editors? Finally, although not directly related to this integrated review, does the NDRP Modernization improve the consistency in product labeling across different agents and same agents manufactured by different manufacturers? Thank you.

DR. CONNELLY: Thank you, Dr. Chalasani, for those really great comments and questions, and we'll be picking up on some of them when we get to the Q and A.

Now it's my pleasure to introduce Dr. Gregory Curfman, who is a deputy editor of the Journal of the American Medical Association. During his career as a medical journal editor, he

previously served as executive director of the New England Journal of Medicine and the Health Care, Policy, and Law editor of JAMA Internal Medicine. Dr. Curfman trained as an internal medicine physician and cardiologist at Massachusetts General and Brigham and Women's Hospitals, and his interest in health law include the regulation of prescription drugs and medical devices.

Thank you, Dr. Curfman, for being with us today and look forward to hearing your perspectives regarding the integrated assessment of marketing applications on behalf of JAMA, and I'll turn it over to you. Thank you.

DR. CURFMAN: Thank you very much, Dr. Connelly.

My name is Greg Curfman. I'm a deputy editor at JAMA. I want to clarify that I'm speaking today as a private citizen and not as a representative of JAMA. I want to direct my remarks to some of the statutory considerations regarding the new FDA integrated drug reviews.

A previous publication in JAMA Internal

Medicine from March of 2020 by Matthew Herder and colleagues contained a concise summary of some of the points that I will be making today if you want a reference to read. When I say statutory considerations, the controlling statute that I'm referring to is the Food and Drug Administration Amendments Act of 2007, often referred to as FDAAA, and specifically 21 USC Section 355(l).

The question that I want to address in my remarks is do the integrated drug reviews comport with the statutory language in FDAAA? A corollary question, is the plain text of Section 355(l) of the statute unambiguous?

The key textual language in Section 355(l) of FDAAA, I have summarized the key points on this slide. The language states that a summary review that documents conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation for any non-concurrence with review conclusions.

The decision document must include a separate review or addendum to the review if disagreeing with the summary review. There must be identification by name of each officer or employee of the FDA who participated in the decision to approve the application, and a scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

So in summary and conclusion, on the basis of the plain text, the 2007 law, FDAAA, assumed the preparation of individual scientific reviews, including disagreements, and was explicit about the need for these reviews, which are the work of individual reviewers, to be published in an unaltered form.

It is not obvious that the IDRs will necessarily comport with the plain text of Section 355(l). If the plain text is deemed unambiguous, FDA's interpretation of the text would not be granted deference. If the content of FDA integrated drug reviews conflicts with the clear

language of FDAAA, the integrated reviews may be subject to scrutiny. And finally, it is essential that the integrated reviews, as a matter of law, adhere closely to the spirit and the letter of the statute. Thank you very much.

DR. CONNELLY: Dr. Curfman, thank you so much for your comments.

Next, I'd like to introduce Dr. Jonathan Darrow, who is an assistant professor of medicine at Harvard University and an associate professor of law at Bentley University. He received his research doctorate in pharmaceutical policy from Harvard University where he completed an LLM program in intellectual property.

Dr. Darrow has lectured widely on issues of FDA regulation and published numerous articles on issues such as expanded access, breakthrough therapy designation, drug efficacy, biological products, and expedited development and approval programs.

Thank you, Dr. Darrow, for your participation in today's workshop and really look

forward to hearing your perspectives. I'll turn it over to you.

DR. DARROW: Thank you very much, and thank you for this opportunity. As you mentioned, I am an academic and I've looked through hundreds of these review documents. The main point that I'd like to make is that it is important to preserve the individual FDA reviewer insights.

The FDA's Federal Register notice and the comments this morning have repeatedly assured us that differences in opinion or dissenting data interpretations will be preserved, and that is a great start. It's not clear to me, though, that that is enough.

For example, if an FDA reviewer points out that a primary endpoint was changed part way through a trial, but that's not necessarily a minority viewpoint or a disagreement, but it may be something that an integrated review might omit. So it is important, in my view, that the review not be sanitized in that way.

Other examples that I've seen, FDA reviewers

might comment about weaknesses in trial design choices that potentially create risk of biases. There may be skepticism of an applicant's explanation for missing data. Sometimes I've seen characterizations such that efficacy was small or modest. There may be descriptions of embarrassing data or procedural irregularities.

So again, these are not necessarily minority viewpoints, perspectives, or disagreements, but my concern is that they might be left out in a holistic approach to the description of the drug.

The other points I'd like to make are much more minor. First, this would apply to any review document whether integrated or not. I've had trouble with text searchability of these documents, and that's including the sample documents that you circulated for this session today.

In some cases, I've seen sentences that break from one page to the next, and the first page is searchable, and the second page is not. In other cases, there are embedded figures that have critical information. They are perhaps on page 320

of a 400-page document. If they're not text searchable, people are not going to find those.

The second minor point that I'd like to make is that if the pages are in landscape and not portrait, they are very difficult to read on a screen. That is an approach that made sense back when people used hard copies. Now that we're using computers, those should be placed in portrait at all times.

Last and again, this applies to any type of review document, whether integrated or otherwise. Please use plain language when describing efficacy. This is from the sample you sent around, "Log10 HIV-1 RNA change in the ITT-E population." That as a measure of efficacy means nothing for the vast majority of the public. Of course this information needs to be in here, but right alongside it, there should be some explanation of what that means and how patients will feel, function, or how much longer they will live, along with an explanation of this scale. Thank you.

DR. CONNELLY: Dr. Darrow, thank you for

your comments, a really helpful perspective, and hopefully we'll be getting back to some of those in the Q and A.

Now it's my pleasure to introduce Ms. Kristin Dolinski, who is the deputy vice president of Science and Regulatory Advocacy at Pharmaceutical Research and Manufacturers of America. In her role, she leads regulatory policy initiatives focused on the human drug review program, innovative tools and approaches, digital health and informatics, and works closely with biopharmaceutical companies and stakeholders, including regulators, on the advancement of advocacy, strategies, policy, positions, and plans.

Welcome, Ms. Dolinski, and thank you so much for sharing PhRMA's perspectives on the integrated assessment of marketing applications, and I'll turn it to.

MS. DOLINSKI: Great. Thank you, Dr. Connelly.

On behalf of PhRMA, thank you for the opportunity to speak today and provide comments on

the FDA's New Drugs Regulatory Program Modernization, specifically the implementation of the integrated assessment of marketing applications and integrated review documentation or the integrated assessment. We commend the FDA for holding today's workshop to hear stakeholder views on the integrated assessment as the agency continues to promote both efficiency and consistency in the review process.

PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested nearly $1 trillion in the search for new treatments and cures, including an estimated $83 billion in 2019 alone.

We support FDA's vision of a new drugs regulatory paradigm, a paradigm that is optimized to identify and resolve key issues, promote efficiencies and effectiveness in drug development,

and is conducive to highly productive and timely interactions between FDA and sponsors. We recognize the implementation of the integrated assessment is a key component of FDA's continued efforts to modernize the New Drugs Regulatory Program and believe it will provide meaningful information to FDA stakeholders.

We believe this new holistic integrated approach to review will support greater consistency and efficiency among FDA's review divisions. We support the integrated assessment and propose the following suggestions for the agency's consideration as they implement the integrated assessment.

We support FDA's efforts to streamline review processes and reduce redundancy, and urge FDA to retain the current level of detail and transparency captured in the current review templates. We note that there is a significant amount of information and level of detail from the interdisciplinary review that is not included in the integrated assessment. More specifically,

information relating to supportive clinical trials such as the review of innovative tools and approaches, protocols, and case study reports are not included. While the new integrated assessment streamlines the review documentation, there is other information that can be important to the understanding of FDA's thinking in its review of new drug products.

We believe that FDA's transparency with appropriate protections for all confidential commercial information in posting action packages for approved products is a critical part of the drug development ecosystem. During today's discussion of the integrated assessment, we look forward to hearing about FDA's own experiences with the new review process. We would like to understand whether the integrated assessment has improved efficiency for the agency and resulted in productive and focused communication with sponsors.

We encourage the agency to formalize the use of the integrated assessment while maintaining the levels of transparency and openness of the review

process previously available to sponsors and stakeholders. We believe that the integrated assessment is a more effective approach to providing clarity on FDA's decisions regarding the regulatory approvals. Again, we thank the agency for holding this workshop today and look forward to the discussion on this important topic. Thank you.

DR. CONNELLY: Thank you for sharing that perspective.

Now it's my pleasure to introduce Dr. Danielle Friend, who is a senior director of Science and Regulatory Affairs at the Biotechnology Innovation Organization. In this role, Dr. Friend develops and advocates for policies that support the development of innovative therapies. Her portfolio includes issues pertaining to rare diseases and orphan drugs; pediatric drug development; cell and gene therapies; digital health technology tools; and PDUFA and 21st Century Cures Act implementation, including patient-focused drug development, and she leads BIO's work related to the opioid crisis.

Dr. Friend, welcome, and we look forward to hearing BIO's perspective on the integrated assessment of marketing applications, and I'll turn it over to you.

DR. FRIEND: Thank you so much, Dr. Connelly.

BIO would first like to thank FDA for the opportunity to provide comments today regarding the implementation of the integrated review documentation. BIO is the world's largest trade organization representing biotechnology companies and related organizations across the globe. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, delay the onset of those diseases, and to prevent them in the first place.

BIO's membership believes that FDA's new documentation constitutes an improvement over the older template and allows for clear delineation of FDA's rationale for drug approval. This help sponsors better understand the agency's thinking and in turn can lead to stronger marketing

applications, more first-cycle approvals, and ultimately benefits to patients in need of new therapies.

The information in the integrated documentation can be used to understand how individual trials were designed, the outcome measures used, and the result of the studies. Increased knowledge sharing can help to decrease development burdens across industry. As FDA is recognized as a leader among other regulators, we would like to especially emphasize the point that many of FDA's review documentations are really reviewed by and looked to by other regulators across the globe.

We do provide the following recommendations to support discussion and for consideration of FDA as integration of the review documentation continues. First, BIO requests that FDA clearly reference information on drug development tools and new technologies used in the context of drug development and review.

We find that across reviews, different

versions of the statement of patient experience, for example, have been used, and different reviews may populate the statement of patient experience to varying degrees. We thus encourage the agency to consider mechanisms to ensure that patient experience data, among other drug development tools and data, is provided in a complete and consistent format to dedicated sections within the integrated review.

We request the FDA ensure that any relevant information is not removed or admitted as the new documentation is implemented. FDA may consider establishing mechanisms that ensure all key information is captured and documented by reviewers.

If information is moved to the appendix of the document or information is not made publicly available, we do request that FDA continue to provide mechanisms for stakeholders to be able to access that information. Additionally, for redacted sections of review packages after product approval, FDA should consider sharing information

with the applicant outside the need for the sponsor to request the information through a FOIA request.

BIO believes the FDA's transparency in posting action packages for approved products is a critical part of FDA's relationship with the drug development ecosystem. In 2018, FDA changed its policy and no longer supports full transparency regarding its regulatory advice decision, and we do request that FDA reconsider sharing some of that information.

FDA should also consider including information on exclusivity, review designation, and use of priority review vouchers as applicable. If the application under review is for a combination product, a summary of any human factor studies or other assessments required by the agency for approval should also be included.

Finally, as technology is advancing, we do encourage the agency to consider providing information included in the integrated review in an electronic format that can be more easily searched across products and/or downloaded by other

stakeholders. Looking forward to the rest of the discussion today. Thank you.

DR. CONNELLY: Great. Dr. Friend, thank you so much for sharing those viewpoints and perspectives.

Now it's my pleasure to introduce Dr. Richard Kovacs, who is Q.E. and Sally Russell Professor of Cardiology also at Indiana University School of Medicine. Dr. Kovacs has worked in industry as a senior clinical research physician at the Lily Research Laboratories of Eli Lily and Company, and he returned to the full-time IU School of Medicine and Faculty in 2003 and served as the associate dean before clinical research, and associate director of the Indiana Clinical and Translational Sciences Institute.

Dr. Kovacs is a past president of the American College of Cardiology, and he has also served as chair of the ACC Board of Governors and held leadership roles on the ACC's Science and Quality Committee and the National Cardiovascular Data Registry Management Board.

Thank you, Dr. Kovacs, for also being with us today and sharing your perspectives regarding the integrated assessment of marketing applications on behalf of the ACC, and I'll turn it to you. Thank you.

DR. KOVACS: Thank you, Dr. Connelly.

I am representing the American College of Cardiology, which is the largest professional society, and we are worldwide, of course, including the vast majority of U.S. cardiologists and cardiovascular care providers. We're a trusted source for how we take care of patients, most importantly. So we look to the information that comes with drug approval critically, and it's important in our development of guidelines for how cardiac care is provided in the United States.

In full transparency, we also partner with the FDA through our national cardiovascular data registries, most prominently the device side with our linkage of our transaortic valve registry with FDA.

This is not the first time we've been asked

to comment globally on FDA policy, and these first bullet points in terms of what we stand for as a professional society also were in our comments on PDUFA and the PDUFA renewals. We support advancing the regulatory science and modernizing the drug safety system, and most importantly incorporating patients and their input into total product lifecycle. Many of you may not know that cardiology is becoming increasingly interdisciplinary and multidisciplinary, so we have interest far beyond what you might consider usual cardiology.

Next slide, which is the meat of my discussion. On the left, by and large, we are in very close alignment with the proposal for this integrated assessment. We have familiarity with interdisciplinary review, and it's not been pointed out the successes of interdisciplinary review of QT issues, which bring the scientists together. I think that's important and that has worked. You're in alignment with our collaborative nature and you're in alignment with our stated goals.

Three potential concerns -- and I'm glad that a couple of these haven't been mentioned, but the groupthink is one where within our society, with all of these major documents, we actually have designated contrarians to contribute to the documents and formalize those dissenting opinions in a summary statement. I did not find much -- and perhaps this will come out in the discussion -- about reflecting the input of advisory committees. We feel that this is very important and very detailed and nuanced discussion.

Finally, I'd also like to hear a little bit more about consistency across timelines, especially for repurposed drugs, and fenfluramine comes to the mind of every cardiologist, and to have consistency across these integrated reviews over time and institutional memory. Thank you for allowing me to participate.

DR. CONNELLY: Dr. Kovacs, thank you. Those were excellent points and look forward to being able to bring some of these up in the Q and A.

Now I'd like to turn it over and introduce

Dr. Eleanor Perfetto, who was named Senior Vice President of Strategic Initiatives for the National Health Council in 2015 and was promoted to Executive Vice President in 2019. She also holds a part-time faculty appointment at the University of Maryland, Baltimore School of Pharmacy, where she is professor of Pharmaceutical Health Service Research. Her research and policy work primarily focuses on patient engagement and comparative effectiveness and patient-centered outcomes research; medical policy development; patient-reported outcomes selection and development; and health care quality.

It's a pleasure to welcome you, Dr. Perfetto, and we're so glad to have you here to share perspectives on behalf of the NHC regarding the integrated assessment of marketing applications, and I'll turn it to you.

DR. PERFETTO: Thank you, Sarah. I really want to express my appreciation to the FDA and all the stakeholders who are here today. It's an honor to be able to contribute.

I want to begin very quickly by just telling, for those of you who don't know about us, a little bit more about the National Health Council. We are a membership organization with five different membership categories. Per our bylaws, the largest category always has to be patient advocacy organizations.

So you see the distribution of logos here on the screen of all of the different patient advocacy organizations that are in our membership, ranging from very large organizations, all the way down to the smaller organizations that represent the rare disease community, a small population of people in the United States that have a chronic disease or disability. We'd like to say that we represent the voice of the over 160 million Americans with at least one chronic disease or disability.

I think, as other speakers have said, we of course support a coordinated review, improved communications among review teams, the streamlined review of drugs and biologics, and a central place for anyone to be looking for information. All of

these kinds of things are very common sense, and I don't think that anyone would refute that these are laudable goals that we should be striving for and that the integrated assessment is one of the ways of reaching these goals. So we're very much in favor of that. I think, as you've heard from other presenters, the devil is always in the details, so we do have some suggestions and some things that we would like to see highlighted.

We would like to ensure, as part of the transparency, clarity, and readability issues that were talked about a little bit earlier, that assessments include a specific section on how patient experience data was considered, and you've heard that from some of the previous speakers also. We'd also like to ensure that the benefit-risk analysis also include a discussion of how patient experience influenced the agency's discrete decision. We believe that these two points really helped to contribute to that transparency.

Everyone needs to remember that in terms of the use of patient experience data in applications,

this is still very nascent and we're learning as we go along. So unless these points are brought to the forefront, it's going to be very difficult for us to tease apart how that information was or was not used and how it was used for an approval or not an approval in order for us to really understand the contribution that that's making. We'd also like to see a user-friendly version, a non-technical abstract or document in layman's terms, that could be available to patients and others to help improve transparency, clarity, and readability.

I just want to point out that the patient experience data form that's being included in applications is very important, and we really don't want to see anything that would deter its use. We really want to see this form being used, and we really are advocating for that.

The only way that we can learn about how patient experience data is contributing to this process is if this form gets used, if it gets filled out, and if the information is indicated as

clearly as possible how the information contributed to the process so that we can learn from this, we can improve the information and data that get included in applications, and we can include the way this form gets used. We can't improve upon it if it doesn't get used and if we don't analyze the data.

So I would like to thank you, and I'm happy to stick around for the questions in the Q&A session, and I look forward to it.

DR. CONNELLY: Thank you so much.

Now I'd like to introduce Dr. Joseph Ross, who is a professor of medicine and public health at the Yale School of Medicine; a member of the Center for Outcomes, Research, and Evaluation at Yale-New Haven Health System; and co-director of the National Clinician Scholars Program at Yale. Dr. Ross co-directs the Yale-Mayo Clinic Center for Excellence in regulatory science and innovation; the Yale Open Data Access Project; and the Collaboration for Research Integrity and Transparency at Yale Law School.

With expertise in health services and outcomes research, and the translation of clinical research into practice, his research examines the use and delivery of higher quality care and issues related to pharmaceutical and medical device regulation, evidence development, postmarket surveillance, and clinical adoption. He has published extensively with more than 400 articles in peer-reviewed biomedical journals and is currently the U.S. outreach and research editor at BMJ.

Thank you so very much, Dr. Ross, for joining us and being on today's panel, and look forward to hearing your perspective on the integrated assessment of marketing applications, and I'll turn it over to you.

DR. ROSS: Thank you, Dr. Connelly. I appreciate having the time to address the group and to speak and make some public comments, but also I strongly appreciate the work that FDA is doing in this regard.

I just want to reiterate, in part, because I

feel like I'm representing the scientific community who uses these documents for so many important reasons, the very valuable and important scientific uses for the rich detailed information that is made available through these FDA action packages. They really are critical to the public health and research community, and that includes work in clinical research; public health research; regulatory science research; health policy research and other policy research; as well as developing patient and clinician decision-making tools for medical product use. I just wanted to make sure that those points were made.

One of the disadvantages of going late is that other people have already made some of the key comments that I was going to make, but I really do want to applaud the efforts to improve these materials -- it really is time -- and I think there are some very clear advantages to these new materials, including clear representation of the FDA's conclusions and a clear overview of the major decisions made during the review process.

I cannot say how much I really appreciated the revised benefit-risk assessment in the two documents that were provided. I thought they were excellent. I really liked the table of experience data, which was just noted. That was new and I thought very useful in terms of documenting how this information's now being used as part of regulatory decision making.

Also, to the comments that were made as part of the introduction, I really appreciate that medical officers do not want to spend the time performing redundant work, preparing and formatting documents, as opposed to doing intellectual work. So it makes a lot of sense to engage a medical editor and others to make these documents.

I appreciate the FDA is now creating these explicit opportunities for agency SMEs to interact with one another across disciplines, so the comments that I'm going to make on my next slide really get to what I think can improve these documents further. This really hinges on some of the points made, like Dr. Kerry Jo Lee's, that

these documents are still going to provide the same level of detail and data.

We only had two exemplar integrated reviews to go through that were provided as templates, so my assessment may not be fully informed, but these were things that I thought were problematic. Seemingly missing was critical information that I had previously used for other research work particularly used in the medical review documents, and maybe I'm just having difficulty locating this information.

For instance -- and Jonathan Darrow noted this as well -- the Table of Clinical Studies information was not available, for one, or maybe there were only two studies that were relied on. But for the other, it was a non-searchable image that was difficult to locate.

The Review of Relevant Individual Trials used to support efficacy from prior action packages, now a lot of the nuance and detail is lost. The CSR summary is very short. There are no figures and tables. This information was really

critical in terms of learning about the trials that were submitted and some of the underlying information: the efficacy data, the safety data, and this detailed information particularly on safety for individual trials to enable comparison to other published work.

Just some other suggestions -- I know I'm out of time -- it would be really useful if these documents include clinicaltrials.gov registration numbers that they were used and linked, that when advisory committee meetings were related to their approval, that those were linked within the documents, so you don't have to go to another site and find them.

Publication links, I liked the list of publications that had resulted from the trials but they weren't linked in any format, so maybe a PubMed ID. And I was surprised to see redactions, even in the clinical study summary, which this information is supposed to be provided by a medical officer. No information related efficacy and safety should be protected. Other people talked

about the concerns about disagreements. So thank you again for allowing me to speak, and I look forward to the discussion.

DR. CONNELLY: Great. Thanks, Dr. Ross, and really appreciate your perspective and comments.

Our final panelist, who I'm really glad to introduce, is Mr. Richard White. Mr. White joined the National Organization for Rare Disorders as a policy analyst in mid 2020 and handles a portfolio that includes FDA, NIH, and CDC issues, specifically issues relating to drug development and review, as well as regulatory and scientific innovation.

He also advocates for NORD policies on Capitol Hill and across various stakeholders. Prior to joining NORD, Richard spent time at the Biotechnology Innovation Organization working on rare and orphan disease initiatives, as well as regulatory processes in the drug development and approval lifecycle.

So thank you so much for being our final speaker and your participation in today's workshop,

and look forward to hearing your perspectives on the integrated assessment of marketing applications on behalf of NORD, and I'll turn it over to you.

MR. WHITE: Thank you so much, Dr. Connelly.

As Dr. Connelly mentioned, my name is Richard White, but I go by Rick since Dr. Kovacs has the honor of being Richard in the group. I want to thank the FDA for giving NORD an opportunity to be on this panel today.

For those of you that are unfamiliar with NORD, we're a nonprofit representing over 300 different rare disease organizations and all rare disease patients around the country. Aside from policy, NORD provides support for our member organizations and patients, accelerates research with innovative programs and grants, and conducts education activities among other things. In discussion of the topic at hand, integrative review document, I want to start with some positive aspects and move along to areas that could be enhanced.

Generally, NORD believes that the integrated

review document represents a marked improvement over the previous method of disseminating review information. From our perspective, the document is much more accessible, the organization is clearly thought out, and the sections are well defined, which makes finding contents easy.

The document has several key features that stand out that are listed here, but I would just like to point out that especially for NORD, the prominence of the patient experience section really helps draw the patient in and emphasizes the importance of patient experience at the FDA. I also just want to applaud the FDA generally. The amount of insight provided is extremely helpful in getting a look inside the process of review, and we hope that this leads to progress for patients.

While there are many more positives, I'll wrap up this portion by saying NORD believes that this document represents profound progress and has incredible potential to communicate FDA's thinking to patients about the role their experiences play in the drug development and review processes.

Regarding areas where improvements could be made, the examples provided in the meeting materials were not robust in terms of patient experience data and analysis. The FDA is increasingly using this template. I believe it was mentioned that 21 versions are in the pipeline, so we'd love to see future iterations include more robust patient experience sections.

As I mentioned earlier, this document has the potential to add a lot of value to patients to see their experience acknowledged and utilized. We believe this information presented in a robust and accessible way will continue to increase patient participation, and here are some ways that it might be achieved, the first being a more robust patient experience section.

For example, all of the patient's experience data submitted in the application, whether it was used or not, could be acknowledged in the section along with the rationale behind what the sponsor hoped the inclusion of the data would achieve.

Next, NORD would like to see a stronger

connection of patient experience data to regulatory decision making. NORD believes that the FDA should include an analysis of the submitted patient experience data similar to other sections in the document. Lastly, NORD asks the FDA to consider qualitatively assessing the data provided in the application.

Another area that could be improved from a lay reader's perspective is formatting adjustments that can make the document more accessible, including working hyperlinks to ensure smoother navigation, hyperlinking the table of contents, and making sure that the links in the document are effective. Finally, NORD hopes that the FDA will consider expanding the designation information aspect of the review. Many of the designations are a result of innovative data collection and add to value for other trial developers.

I conclude by saying that from the NORD perspective, the integrated review document represents great progress and has a lot of potential, and we believe this information,

collated and organized in a robust and thoughtful way, could lead to better clinical trial development, increased patient engagement, and hopefully more first-time approvals. Thank you again for the opportunity to speak today, and I look forward to the Q and A.

DR. CONNELLY: Great. Thank you so much, and thanks to everybody. This was a great framing of really insightful feedback that we, as those who are invested in the integrated assessment, really value hearing, and we'll take back.

I'm going to turn it now over to John to start off the Q and A.

DR. FARLEY: Sure, and thanks, Sarah, and thanks again to the panelists. Your input was incredibly valuable. This is an effort that in addition to thinking about the presentation of the scientific data, there's a lot that goes behind this. We have a very big training effort going on within OND for reviewers around the review process, and then we also have technical folks in the background backing us up. We're not Amazon, but we

have good technical folks, and you've highlighted a lot of issues, drawing those to our attention, which is really valuable.

I wanted to check in with the panel because I know that we have a limited time. I'm going to propose sort of a rough road map for the next 45 minutes based on some overarching themes that we've heard. I think the first theme to tease out might be the issue of detailed transparency and independence. That's a theme that I'm hearing; second, the patient perspective and integrating the patient perspective as theme two for our discussion.

There are some issues checking in with industry, who is the key stakeholder here, and that will be number 3. As a physician, I really care about this data being usable for clinical care guidelines, so some themes there to talk about, as well as researchers.

Any other topics that the panel would like to make sure we get to or is that roadmap acceptable to everyone?

DR. CONNELLY: It sounds very acceptable to me.

DR. FARLEY: Great. Okay.

Well, let's jump right in. There have been a lot of input regarding detailed transparency and independence for reviewers. I wanted to start out by giving you my perspective as a signatory and explain to people what a signatory is.

The Food, Drug, and Cosmetic Act, as many of you are aware, authorizes the secretary of HHS to approve or not approve a new drug or biological license application, and that authority through delegation memos is down-delegated to various levels within FDA. For a new molecular entity NDA or a new BLA, that signatory authority down-delegates to the office director, and I'm the office director for infectious diseases, so I've done quite a few of these.

Generally, an office director would have a portfolio of easily a half dozen applications in process simultaneously that they need to make a decision about. The reviewers at the FDA, their

output ultimately at the end is to make a recommendation to the signatory authority regarding the approvability or non-approvability of a drug.

One of the innovations, which I was excited about as a signatory, is the issue of elevating review issues very early, identifying and elevating them early in the review process. I think Sarah can walk through the process a little bit, but there is a benefit-risk scoping meeting now that coincides with the filing meeting, at which the review team is invited to identify review issues based on their initial review of the application. Of course, they can identify issues later.

I guess I wanted to pick up a little bit on Jonathan's points and also raised by others. Let's focus on, say there was a change in the primary endpoint for one of the pivotal trials, so one of the adequate and well-controlled trials, supporting efficacy and safety for the intended use, and they change the primary endpoint in the middle of that.

We think that that's obviously very important. Our view of the new process is that

that should definitely be considered as a review issue and should be elevated by the reviewer very early in the review process. That should have come up at the benefit-risk scoping meeting, or if it's discovered later, be brought up immediately in what we call joint assessment meetings, which happened regularly throughout the course of the review. One of the things the process does is it brings the signatory in early.

I started at the agency nine years ago and, really, I had to pay close attention to what was going on in the team, but it would be totally possible in the old system for me to not be aware of that until one month before the action, that there had been a change in the primary endpoint, totally possible.

So the thought was that that would become a review issue and focused on early, and there would obviously be two key disciplines that would have to be engaged in discussion. That would be biostatistics, then there would be the clinical reviewer, and there may be others depending on what

it was, and that the detail around that review ought to be captured sufficiently in the integrated assessment portion of the review, but then also detailed in the appendices.

So hearing that, maybe start with Jonathan and invite others. How could we make that better? Do you think that's an improvement? Do you think it's not? Do you agree with me; do you not? So I'll stop there and maybe invite Jonathan to start.

DR. DARROW: First off, thanks again, and I do think that the integrated review has some advantages in terms of reducing redundancy and greater efficiency. I'm not sure that changing the primary endpoint just part way through the trial was the only thing I was talking about.

In fact, if I'm recalling correctly, this was from the Luxturna review document, where they had changed the primary endpoint at some point during the development process. It wasn't necessarily part way through the trial, but that detail may have been left out, and it was changed from the normal measure of visual acuity to this

custom-made scale that was created just for the approval of this drug. That was nowhere else in any of the other reviews. It was just on page 320 of one of the review documents. In an integrated review, my concern is that that's not going to be there.

DR. FARLEY: Yes. I guess what we're training to -- and certainly my expectation as the signatory is that I better be hearing about that once the primary reviewer realizes it's an issue rather than putting it on page 320 of their review because that isn't serving the American public well if the people making the decisions aren't aware of the issues.

So that's sort of what we're trying to do. I think there are considerations many of you have around reviewer independence, so we can talk about that a little bit more in a minute. I'm wondering if there are others on the panel that want to come in here with a perspective.

DR. ROSS: John, this is Joe Ross. Thanks for opening it. Maybe I can just touch on this

point that Jonathan and you were just discussing around the primary endpoint. I can speak as a journal editor, and I'm sure Greg can address this, too, that when there is an endpoint change, we hunt through clinicaltrials.gov to try to figure it out in the context of considering a paper for publication.

Where do you think this information will be found? If it's part of the pivotal trial and that consideration, where will it be discussed by the reviewer? Will it be down in the CSR summary? Will it be up top so that it would be obvious to any individual reviewing the pivotal evidence that this was an endpoint that shifted during the course of that?

For me, it's helpful just to understand where you expect this information to be clarified. I do think the integrated review document offers a great opportunity to make information more findable. What Jonathan is describing and what I've experienced, it's a little bit like hunting through a haystack for that needle to find the key

details. So I'm just curious. Where do you expect to put that information so that we can all know where to find it?

DR. FARLEY: Yes. For this particular example, I would have expected that had the reviewer had time, and they usually would -- because the nice thing about the new process is that we've got about 8 weeks before filing when the application comes in, and that really gives -- we're not just sitting there for 8 weeks. Actually, we're front-loading the review, and that's the goal of this. We get a better scientific process if we front-load the review.

So our expectation is the reviewers are digging into that immediately and starting their review of the individual trials in earnest, for example, if it's a clinician or a statistician.

I would have expected that to be brought up at the benefit-risk scoping meeting as a potential review issue, and as we talked about it, we would have likely decided it was going to be a review issue in the integrated assessment portion of the

template, in which case it would be a review issue with respect to assessing benefit.

So it would be in that section of the review, and we would have planned who was going to write that, and probably the two key writers would have been the clinical reviewer and the statistician in that case. We would have made an assessment and a disposition. And I'll walk through another example in a minute, but hopefully that answers your question, Joe.

DR. CONNELLY: John, may I add just one more opportunity to what you so nicely laid out? Several of you touched on the fact that drug development extends over a life cycle. So this process is emphasizing, as John mentioned, early identification of review issues, potential review issues to the extent that they're known, and we even encourage coming together earlier than when an application is submitted, even at the time of a pre-NDA or BLA meeting.

That is an opportunity where the review team, exactly as John described, with all the

disciplines and the vision signatory come together, and we are emphasizing that that is a time to bring forth known issues from ongoing development to start to identify what those potential review issues will be if an application gets submitted. So even by the time and application comes in, there's already been a discussion of what might be some issues that will be a focus as the review unfolds, even before the benefit-risk scoping meeting. So I just wanted to layer on that point.

DR. FARLEY: The other thing, Joe, just to pick up on, depending on what the team ended up -- the discussions in the course of the review around this change in the endpoint, it could very well go to the benefit-risk assessment if it was elevated to that level, so then you would see it there.

I'm going to walk through another example where it's a little bit more clear. In this case. I think it's a question of how significant that endpoint change was; how was it handled; were they blinded when they did it, the whole thing. So

those discussions would have taken place.

DR. DARROW: Can I just add that in the case of Luxturna, again, I don't think the change happened during the phase 3 trial. This happened earlier in the clinical development program. So it's important that as a member of the public, I want to know that they didn't select visual acuity as an endpoint, which would be the normal endpoint you would expect for an eye therapy, because they started with that, and it didn't look good in early trials. That's important to know. But I'm just concerned that that might not be elevated as a review issue if from the beginning of the phase 3 trial they start with a different endpoint.

DR. PERFETTO: John, I want to add to that because I think it's also very useful to know if there were decisions made, especially before the trial began, to change the endpoint to something that's really not responsive to what patients say is most important to them. So it's then traditionally another endpoint, but they're going to go about it a different way in this particular

program because they actually did the groundwork and all of the qualitative research that needed to be done to understand what patients thought was very important to them.

DR. FARLEY: No, I think those are very good points. One of the things we focused on through training and through the development is fine-tuning the role of the clinical reviewer versus the statistical reviewer in the assessment of efficacy because that is kind of related to the themes you brought up.

What we're trying to train to and what we've set up a template to do is we don't need the clinical reviewer to redo a statistical analysis that somebody else actually has a doctoral degree in how to do properly, but what we do need the clinical reviewer to do is to tell us what the clinical benefit is of the statistical finding; what are the clinical implications of the finding?

Jonathan, I really appreciate your point because I think some of this does happen before the NDA hits the door, and capturing that history is

very important. So our training folks are on the phone, and we're capturing your perspective because I do think that that's very valuable insight.

DR. FRIEND: John, do you mind if I just add maybe a piece that's a little bit connected to the transparency piece?

DR. FARLEY: Go ahead.

DR. FRIEND: BIO members recognize that there's a lot of information that's maintained around engagements between sponsors and FDA in the context of milestone meetings. Some of the information that is no longer included is discussions around labeling or postmarket commitments and postmarket requirements. So we did want to raise that as an area where there could potentially be a little bit more transparency.

One other thing that we could have mentioned in our discussions with our members is around information that's provided after product approval. I think I alluded to this in opening remarks. For example, some information is redacted around CMC for intellectual property purposes, but it would be

helpful if that redacted information was provided to the sponsor so that they could take a look and could see what was provided there regarding CMC and other areas that were potentially redacted in the documents that were made public.

DR. FARLEY: Great. We'll take the redaction comments as input, and as you see, Nancy's on the panel. I think we won't respond at this point just to keep us on track, but you've brought up another really good point around this process and the interaction with what we call the applicant at this point, which is the pharmaceutical company who owns the asset which is under review.

What we should be doing and what we're trying to train to is that the mid-cycle meeting, which is going to happen, you will become aware of those review issues certainly by the mid cycle. The mid cycle is also front-loaded in the process; it doesn't happen exactly midway through the review. It's fairly early. The idea is to allow the sponsor to know that information because it

also, I would think, helps the sponsor to contextualize the questions that they're getting from us, which are called information requests, the labeling concerns that we're expressing and the requests we're providing for postmarketing commitments and requirements. The idea was to have a broader discussion and a broader perspective on those.

I wanted to turn a little bit just for a few minutes to the issue of scientific disagreement and how that plays out. Just to close with, I think someone mentioned minimizing issues, and my role as a signatory is to actually elevate those issues and to empower the reviewer who's bringing them to the table to articulate what the concern is. So I see it as elevation rather than minimization, but that's just my perspective, and if I'm not doing that, I'm not doing my job.

Let's talk a little bit about disagreements. I was just involved in a review where these disagreements often don't have to do with approvability or non-approvability, but they're

substantial. How should the indication be framed? What population should it include? We did have such an example, which is being redacted now, so I can't talk about it publicly. But there was one perspective among disciplines that the indication should be fairly broad and another group of reviewers who felt there was some narrowing that was in order based on the data that had been submitted.

That should be, of course, a review issue, and actually very much goes to a benefit-risk framework issue. Those are head on. The way we structured the review issue summary is the perspective of each group, and then ultimately, the signatory has to make a decision. So then the third section is what was the signatory's perspective on resolving the issue.

In addition, there is more detailed information supporting the perspective of each group in specific reviews in the appendices. Reviews in the appendices are owned by a discipline rather than a group. It may be the group of

pharm-tox reviewers, for example, who write it together, but there are individuals in the appendices.

So let me just throw that back to the panel and see what they think of that approach. I know you don't have a great example in front of you, but that is what it's going to look like. So I'll stop there and see if folks want to come in.

DR. CURFMAN: John, this is Greg Curfman. I'm sure you're aware, and others, too, and certainly Joe is, that medical journalists, we undertake pretty intensive reviews of manuscripts. Each of our manuscripts at JAMA will receive four or more reviews if we're seriously considering that manuscript, and the amount of disagreement among reviewers can be really extensive.

So a lot of the job of the editors is to sort through all of the detailed reviews, identify the disagreements, and of course ultimately come to a decision, but retain those individual reviews in our files as part of the record.

It's so extremely important because it's

that disagreement that is so incredibly helpful, and the rich detail really shouldn't be lost. I imagine that your process is quite similar in that regard, and the importance of that detailed information and the disagreements I'm sure is equally important, if not more important, at FDA than at the medical journals.

DR. FARLEY: Yes. We appreciate that, and having spent 20 years in academics, I've been on the receiving end of manager overviews, and sometimes they're so disparate that your head is spinning and you don't quite know what to do as the author, as the author of the manuscript, so I appreciate that.

Yes. No, I totally agree with you, Greg, and I think that's a training need at the agency. I think one of the things this new process does is normalize disagreements because before this, when reviews were taking place within certain disciplines, there kind of becomes a camp-like approach where this is our perspective, and this is somebody else's perspective, and we're just going

to put it in our review, and the poor signatory has to sort it out in the last month.

So the idea is a balance. I think the appendices are much longer than I imagined they would be, and that's good, because I think that I want to see individual review work so that you have enough sufficiency of detail. We're still working through that, but that is certainly our intention.

DR. ROSS: This is Joe. I would just echo that, and I think those appendices are really going to be critical. While of course you don't want to see the clinician reviewers re-doing all the work of the statistical reviewers, you still want to be able to see some of that work of the statistical reviewers to be able to see the data, see the figures --

DR. FARLEY: Right.

DR. ROSS: -- and see the independent reanalysis.

I think that there's a little bit of a bugaboo about disagreements. I mean, disagreements are good. That shows that people are thinking

about it, and bringing their own perspective, and then someone's coming in resolving them, and there's a plan laid out to how to manage them. So I think they are normal and they should be normalized. It's critical to see why one person disagreed and didn't and what actions being taken in consequence.

DR. FARLEY: Right.

Jonathan, did you have a point?

DR. DARROW: Another issue that Joe just reminded me of, which is it's not always clear, to me at least, how much of the 400-page FDA review documents are cut and paste from submissions by the applicant. If there's a way to lay that out more clearly or if you can assure me right now that none of it comes from the applicant, that would be --

DR. FARLEY: It's a challenge for me as a supervisor as well because we don't want that. Part of the beauty of the integrated assessment is that it's a tabula rasa, and it doesn't lend itself to cutting and pasting. It's not what were the inclusion/exclusion criteria, and even the

statistical analysis plan section, our biostats folks who were engaged in developing this, because this truly was a multidisciplinary effort from everybody who's engaged in CDER and was to try and avoid making that easy to do.

So I appreciate your point. I don't think we're there yet, but it's where we want to go as well. I totally agree with you.

I think it would be good, just mindful of the time, that we go ahead and turn our attention to the patient perspective and incorporating the patient perspective more effectively.

So Sarah, I'm going to turn this over to you at this point.

DR. CONNELLY: Great. I think we've heard from almost all of the panelists on the critically important issue of incorporating the patient perspective throughout all stages of drug development, and for the purposes of today's panel, in the review of marketing applications.

I've heard through the comments that having the patient experience table is valuable. I also

heard from Eleanor that she acknowledged that this table is in a nascent stage. So I'm just curious to hear more from you all as panelists, how it is used by you, how you see the integrated review as facilitating incorporation of patient experience with this table in advancing that goal of including the patient perspective into drug development, and maybe expanding more on some of the points that you made -- I know that everybody had a pretty abbreviated time during their talks -- of what is important for us to hear.

As we continue to look to iterate and refine the integrated review, what else we should be mindful of that we can include and enhance, not only in the template, but also I think what I've heard is in some of our training about how things related to patient perspective are incorporated in how we are communicating benefit-risk or things like that, so we have number of perspectives.

I'd like to start with the patient advocacy perspective, and maybe, Eleanor, I'll start with you.

DR. PERFETTO: Sure. I think from our perspective the patient experience data form is important in that we don't want to see the integrated review form a barrier to people using it. They have so many other things that they're thinking about now in a different way that they might neglect putting any information in there just because they feel like they don't really have the time or it's not making a big difference, so why would I put it in there and use the time that way?

We want to avoid that barrier. We really want to see the form get used. Right now, as I said earlier, it's pretty nascent. The form does not get used regularly. We'd like to see it used on a regular basis so that we really can learn from what's going on that form. I've been a participant in many discussions that say the form needs to be changed, it needs to be altered, and all things need to be done to it. And my response to that is, until we can figure out what we're learning from the form and what we're not learning from the form, how do we know how best to change it?

So we have to get the reviewers to be using it. We have to encourage its use. We have to do everything we can to support its use so that we see the data that gets collected there; how useful it is; look at the alignment between what the reviewers are finding and the alignment between what's actually in the application; how it's being used, and learn from all of those experiences. We're just beginning to scrape the surface of that.

Externally, if you're not within the FDA, you only see those forms that are completed that are for approved products. You don't see the ones that are completed for not approved products. So I would like to see the FDA actually making some efforts to take a look at what's going on with those forms, especially to get full the breadth of what's going in there and not just approved. As we saw in the two examples that were provided to us, one was blank, nothing was in there, and one had some patient-reported outcome information, but it was at a very small level. There really wasn't any detail.

So I think I'll just summarize by saying we want barriers removed to using it. We want to see encouragement to use it; as much information as possible; how was it used; and how was it included. We even go as far as to suggest to companies that when they're submitting an application, they fill it out in advance, show what they have done or what they believe is important, then a reviewer can critique that and say I disagree or I agree. But rather than having those turn up blank, we want everything possible to encourage its use. We can't learn more about the impact of patient experience data until we have information from that form or variations on that form in the future to inform that decision making.

DR. CONNELLY: Great. Great points. Thank you.

Rick, I'll turn to you. Do you have anything to add from NORD's perspective?

MR. WHITE: Yes. I think I just want to echo a lot of what Eleanor just said. I think that was fantastic, especially in regards to there's no

such thing, where we are in this universe of data collection, as not helpful data. Anything that gets submitted has value to produce a distinguished barrier between what is helpful and what is not.

I also think that there's a place for including analyses for the patient experience section. I think it could be fleshed out to be similar to other sections where there is more of a train of thought or narrative around why this data was used and what is the value of it.

I think that there's also the potential to include other sources of input in the patient experience data section if there was a Voice of the Patient meeting, or an externally-led PFDD meeting, or an AdCom. These could all be integrated into that section around patient experience.

DR. CONNELLY: Great. Thank you.

DR. PERFETTO: Can I add to --

DR. CONNELLY: Please.

DR. PERFETTO: I think one of the things that could be incredibly valuable that reviewers may not be encouraged to do is if they know about

patient experience data that exists and the application doesn't refer to it, that's just as informative as pulling data out that is in the application. To say that they know Voice of the Patient meetings took place, or externally-led meetings, or other kinds of data that are out there were not used in the application, that can be a contribution.

DR. CONNELLY: That's a really good point. Thank you.

I know we're short on time. I do want to get at least one or two other perspectives on this.

Danielle, I made a note from your presentation about patient experience being populated differently, so I'd just like to hear your thoughts on this.

DR. FRIEND: Sure. Absolutely.

I think Eleanor and Rick did a great job of laying out some of the things that we're hearing from industry as well, but when we've taken a look at some of the statements of patient experience or the patient experience data table, there is

variance in how much they're populated. Some of them will reference other sections of the review document for more information. Some of them will reference Voice of the Patient meetings and some won't, even though there was a Voice of the Patient meeting that actually occurred on that particular disease area.

So we think it could be helpful to perhaps outline some core information that reviewers make sure to include either in the patient experience data table or other sections of the multidisciplinary review, and think about ways in which we can integrate the questions pertaining to core information so it's a part of the reviewer's workflow to make sure the information is included; so things like description of the patient experience data; the study design or objectives; how is the data considered; and if it wasn't considered, why does the FDA have issue with the data?

I think particularly for industry, everyone is very eager to collect patient experience data,

but we're all still learning, and oftentimes industry will look at these review documents to learn so that they can better implement collection of patient experience data as they go. So making sure we're being comprehensive about how the FDA considered that data I think is really important, especially for the industry perspective, so we can use learnings and make sure that we're improving over time.

DR. CONNELLY: Great. Thank you.

I know we want to turn our attention to a few other themes that John outlined in our roadmap, but before we leave this, to just open it up if any other panelists have thoughts or perspectives to contribute before we move on.

DR. KOVACS: I'll just say from a subspecialty --

DR. CONNELLY: Great. Thank you.

DR. KOVACS: -- standpoint, the patient experience, as I said, the college has been banging this drum for over 10 years and eagerly waiting to incorporate this, either into our guidelines or to

our consensus decision pathways about how to handle the patient. Whether it's from a primary cardiovascular disease standpoint or whether it's from a different disease standpoint that may have cardiovascular complications of the therapy, having objective information from the patients at the patient level is very important and we haven't seen it, and we've been asking for it for a decade.

DR. CONNELLY: Great. Thank you for that.

DR. FARLEY: Great. Thanks.

DR. CURFMAN: This is --

DR. FARLEY: Oh, sorry. Go ahead. Someone was about to speak.

DR. CURFMAN: This is Greg Curfman. I can just add, from my perspective at the medical journal, I see a lot of clinical trials in the work that I do, and increasingly we are seeing more and more patient-reported outcome data being incorporated into the manuscript summarizing clinical trials. So I think this is a very good trend.

I think over time we're going to be seeing

increasingly rich data sets emerging from clinical trials based on patient outcomes, and this is really objective information, quantitative data, not qualitative data. So I think it's really worth keeping an eye on those parts of published articles, and pulling them out, and highlighting them in the FDA reports.

DR. CONNELLY: Great. Thank you for that comment.

DR. FARLEY: Fantastic. I just wanted to spend a few minutes touching on the industry perspective. We will have some industry speakers coming right up in the next session. But one of the things that actually the FDA wanted to ask industry -- and I don't know if we have the right folks on the panel.

But one of the challenges, of course, in implementation is collaborative writing, identifying a section of a document and figuring out how you're going to end up with a work product. I think it places at the FDA a lot of responsibility on team leaders who are finding

themselves also orchestrating writing, assigning different sections to different reviewers, et cetera, and then trying to harmonize.

One of the things that the writers do, because I think that came up earlier, is they are not there to fix the science. They actually are there to try and get the document reading as one voice. Also, I think they're hearing the plain language request from you, and that's something that they could certainly consider as far as suggestions.

So from your experience in terms of collaborative writing efforts, and industry has been doing this for a long time as they prepared submissions, any thoughts or suggestions for the FDA from your experience?

MS. DOLINSKI: Hey, John. This is Kristin from PhRMA. I can just say that is something I can definitely take back. I don't have a specific answer to that question right now, but it's something I can definitely take back to our members and consider for inclusion in our comments in

December.

DR. FARLEY: Great. We appreciate that.

DR. FRIEND: I'm happy to take that back as well. I think in having discussions with our members, I think the key theme that came up is making sure that we're being complete and responsive. I think less of making sure the text looks like it's written by one person, but making sure that the key elements are included. So that's something that I would emphasize, but happy to take this back and see if there's more feedback from our members.

DR. FARLEY: Yes. And certainly a training theme for us is as you're coming up with a document, making sure that minority voices are not underemphasized and presenting it fairly and objectively as the review is prepared. So that's something that we're very much focused on and aware of. Good.

I wanted to ask Naga, maybe to start with -- I'd like to turn our attention a little bit to this work product and how it informs clinical

care guidelines because those guidelines make a huge difference for physicians and patient care. So maybe we could focus on that a little bit, are there things that we can do better. In my field, I work in infectious disease. AASLD has been at the forefront of helping really revolutionize care for hepatitis C largely based on data.

So maybe, Naga, I can invite you to make a few comments.

DR. CHALASANI: Thank you. I think a couple points. One is the executive summary, where there is emphasis on risk-benefit, is one area that I think when we put the guidelines together, I think we look up to -- that's one other reason I think Jonathan touched on, is the key endpoints are expressed in a way that the general public can understand, not just the authors or people who have statistical backgrounds.

Those are two thoughts. But I think otherwise, sometimes we obviously look at these reports to see what is beyond what's in the package insert. I think one danger is that clinicians just

look at the package insert and not quite dig deep enough, but at least the practice guidelines authors are there, so I think this will be an important area that could strengthen the practice guidelines, thus clinical practice.

DR. ROSS: John, maybe I could just jump in with a related point as someone who is very involved in the literature and transparency around this information. The trials that support these approvals, 90 percent of the pivotal trials get published and 60 to 70 percent of the other kind of phase 2 trials get published. That's still a lot of information that the FDA relied on that otherwise doesn't make it out into the literature and doesn't necessarily get reported on clinicaltrials.gov despite the law.

That's why I keep banging the drum on making sure there's enough information in reviews. Sometimes the FDA medical officer is the only one who's seen the trial date outside of the company, making sure that it's reported out and linking to the clinicaltrials.gov registration number or the

publication when possible. So it makes it easier for those of us in the research and evidence synthesis community, including guideline writers, to aggregate all the information that's relevant.

DR. FARLEY: I think that's --

DR. KOVACS: And I'd pile on, on that, as well. I think the point that's been made about the ability to link, I have an entire lecture that I give on discrepancies between the data that's in the label and the data's that's published in medical journals, often revolving around safety, and that's really not publishable data, all those reports of toxicities.

So I think the linkage back and forth in this document is going to be very important to its success going forward, especially in terms of its ability to influence guideline development.

DR. CHALASANI: Can I make a point? Once again, this sort of layers on what Jonathan has said and others have said. When the authors of guidelines are looking at these, I think having the patients' related items, as well as the minority

disagreements, prominently in a predictable location I think would help us as opposed to -- many of us are just not experts at looking at these documents the same way, let's say, Jonathan. I think that's one suggestion.

In a way, though, I think you can help us to look at the documents to help the public. Right now I just don't think we do a good job just because we don't know where to look. Sometimes it's not there, so I think that could be helpful.

DR. FARLEY: Great. A couple of themes that I'm taking away from this, which have been very helpful, I think Richard mentioned the importance of safety data. What we tried to do in the design of the template was make sure that the comprehensive safety assessment was pretty much preserved intact. There's a standard format for that.

So we have worked very hard and, obviously, also elevating safety issues that might not have been obvious to the reader in the old template system. I think that elevating them to review

issues certainly helps and keeps the team really focused and making sure that we're not missing something big. So that's very valuable.

I think I'm also hearing the importance of the trials that we don't consider adequate and well controlled but are important, that aren't pivotal to the efficacy data but actually are quite informative. So I'm taking that away and really appreciate that perspective from Joe and others.

We've heard some usability issues and searchability issues, and folks on the phone are listening to that who can actually fix that. Other issues for researchers, as we close out this session, themes that you want to emphasize, that you want to make sure that we've heard.

DR. FRIEND: Maybe one quick thing that I'll mention, just one of the last comments I made in my opening remarks was in regards to having the format for the information included in the integrated review. Many of our stakeholders actually will compare one review to another, so thinking about other ways in which the information can be shared

besides PDF I think could be really helpful in allowing stakeholders to kind of analyze the information, especially across reviews.

DR. DARROW: If I could make just another quick comment about some information that would be helpful to include, which is the expedited programs and the regulatory history, I think some of the FDA documents lay that out very clearly, and of course there's the summary at the end of the year that lays that out very clearly. But if that's in the integrated assessment, right on the front page right after priority, you could say, "Fast Track 505(b)(2)" and so on. I don't think that would be difficult, and it would be helpful for us.

DR. FARLEY: That's very helpful. And for knowledge management at the FDA, we're looking for those tags as well, so thanks for that.

MS. DOLINSKI: I'll just note and stress that we do feel that additional -- I know we've discussed it earlier, but including extra or additional sections on discussions, or sections dedicated to review of innovative tools and

approaches such as the review of biomarkers and COA tools, or non clinical and clinical trial design and the FDA's approach to data analysis, is a key feedback that we've heard from our members.

DR. KOVACS: John, just one other comment in terms of the research. I'm aware now of some trials where an entire platform -- this is in neuro -- where a single control group is being used for multiple unrelated drugs and how that will be linked, and consistency about understanding that this is the same control group that was used for drug X, drug Y, and drug Z, as you mentioned, because there are a lot of novel trial designs that are going on right now, and they may not be terribly evident to people reading a single article in a single journal.

DR. FARLEY: That's very helpful.

DR. ROSS: John, I'll make one last comment, and I've made a bunch throughout about the use to researchers and others in the clinical community. Most of what we've been talking about is the integrated review document for the original NDA and

for a new clinical indication, but I presume that this is going to be adopted for supplemental clinical indications, where not only trials will be used, but perhaps real-world data and thinking about how this information will be aggregated. I don't envy the work that you guys will have to do on your side to standardized a lot of that information, but it's going to be important as well.

DR. FARLEY: Absolutely.

Great. Well, what I'm going to do, I want to thank all the panelists. I thought this was a great discussion and really super helpful input that we will take back. I'm going to thank you, and I'm going to close out this session, and the next session will be facilitated by Rhonda Hearns-Stewart. I know we have two speakers that have some really good presentations that we're looking forward to hearing.

So I'm going to turn off my video and ask Rhonda to take it over.

DR. CONNELLY: Thank you all.

Open Public Comments

DR. HEARNS-STEWART: Good afternoon, everyone. As part of the Federal Register notice for this virtual workshop, we solicited public feedback on how the integrated review can continue to support stakeholders. We would like to thank Ms. Emily Huddle from Gilead Sciences and Mr. Jason Lipman, representing the Combination Products Coalition, for submitting a request to share their feedback during today's virtual Workshop.

I will now welcome Mr. Jason Lipman, director of Global Regulatory Affairs Devices and Combination Products from Sanofi.

MR. LIPMAN: Hello, everyone. Thanks for the introduction, Rhonda. As noted, I'm Jason Lipman. I'm representing the Combination Product Coalition. The coalition is a group of leading drug biological product and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with the FDA on issues affecting combination products to

advance our common mission, providing the best possible health care to patients. Thanks for giving us the opportunity to speak today.

While the CPC supports the integrated review template and acknowledges the value of implementing a system that effectively communicates the basis for new drug approvals, we're concerned that the proposed integrated review template will lack the level of detail currently provided in the publicly available discipline-specific review memos.

CPC members regularly reference these review memos for combination products to better understand the agency's current thinking on a variety of combination products submission requirements. These review memos may include justifications for why a specific request has been made and would typically provide insights regarding the types of responses that FDA finds acceptable for a given request.

As such, CPC strongly requests that as FDA implements the integrated review document, the discipline-specific review memos remain publicly

available to ensure full transparency and understanding of the agency's current thinking with respect to combination product requirements. This information is particularly important as policies and regulatory requirements for combination products continue to evolve.

Furthermore, although CPC members are most concerned with combination product related information, our member companies are also interested in continued access to all information currently made publicly available following a drug or biologic approval, and this information includes, but is not limited to, presubmission correspondence; inquiries and responses; the review memos of course; and inspection report summaries or decisions to defer inspections.

Allowing the extremely informative discipline-specific review memos to remain publicly available has several advantages, which include that they clarify current FDA expectations for required content and testing as applied to product-specific cases, providing details that go

beyond issued FDA guidance documents and international standards, and that they facilitate more complete filings, which leads to fewer FDA concerns and shorter FDA review and approval timelines, thus reducing time to market for combination products.

The proposed integrated review assessment also has advantages as have been noted. The assessment should help to eliminate duplication of content and should make location of information easier. However, since the two example reviews provided in advance of this meeting had only minimal combination product related content, it was difficult for CPC to comment on FDA questions related to location and use of the information.

CPC has several suggestions on how the proposal could be improved for combination product and delivery device related information. We'd like FDA to provide review memos for all supplements for new and modified delivery devices. That's not always the case.

There should be a specific section for

combination product and device related content, which includes summaries of combination product related presubmission correspondence; combination product related information requests, including the reason for the request, who originated the request, the sponsor response, consulting reviewer feedback and resolution; combination product bridging and leveraging along with the determination of acceptability or non-acceptability; summaries of combination product clinical requirements and submitted clinical data or why clinical data was not necessary; summaries of human factors requirements along with submitted human factors data or why human factors data was not necessary; and other key information that includes summaries of delivery device requirements; essential performance requirements for these devices and combination products; design verification and validation activities; CDRH and DMEPA review checklists; release testing; quality system related information; manufacturing information; and labeling requirements.

That actually concludes our comments. Thank you very much for your time. Appreciate it.

DR. HEARNS-STEWART: Thank you, Mr. Lipman, for your insightful comments, your feedback, and your suggestions. We will definitely take these into consideration as we continue to expand the scope to other types of marketing applications and as we continue to refine our process and template. Thank you very much.

MR. LIPMAN: Great. Thank you.

DR. HEARNS-STEWART: You're welcome.

I will now like to introduce to you all Ms. Emily Huddle from Gilead Sciences.

MS. HUDDLE: Thank you. Hello. My name is Emily Huddle, and I appreciate you extending an opportunity for me to speak today. I work in global policy and intelligence for Gilead Sciences. Gilead Sciences is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need.

I've been asked today to provide feedback on

the following topics and questions related to the new integrated review format. I have worked for over 20 years in the pharmaceutical and biotech industries, 12 of which have been in the area of regulatory intelligence. The definition of regulatory intelligence, for those of you that aren't familiar with that area, is listed and taken from US DIA reg-intel working group, and the diagram to the left highlights some of our key areas of responsibility.

We are focused on the external regulatory environment based on publicly available information in order to apprise our reg affairs colleagues of relevant changes. In the U.S., an important source of regulatory strategy information comes from the summary basis of approval documents; thus my invested interest in the topic today.

Prior precedent is a common query I'm asked to research from my colleagues. Based on a past regulatory precedent, this can provide valuable information, namely to drive the planning of regulatory strategies while also avoiding past

failures. The FDA review documents associated with product approvals can be an invaluable source of this type of information.

This slide highlights some of the questions I'm asked to research based on information contained within the competitor summary basis of approval document. Specific safety signals for certain type of therapeutics and how they -- is there a slide before this; slide 5? Maybe the slides got reversed.

Using databases, I was able to find eight examples of reviews that have used the integrated review template. The metrics I've included indicate a good mix of original versus supplemental applications and standard versus priority reviews across multiple therapeutic areas that also include a couple examples of fixed-dose combinations. I believe this provides stakeholders with a good subset from which to evaluate.

There is a slide that's missing, but I do want to speak to it. This slide highlights some of the regulatory questions I'm asked to research

based on information contained within the competitor's summary basis of approval document. That includes specific safety signals for a certain type of therapeutic and how they were addressed; opinions from specific reviewers and past reviews; examples of how the use of real-world evidence might have been proposed by a sponsor and whether it was accepted or not by the FDA and why; and then similarly, information on the acceptability of specific drug development tools such as biomarkers or clinical outcome assessment.

So you are likely wondering how I'm able to find this information across all posted reviews on the FDA website, and there are external regulatory intelligence data bases that enable these types of searches, searching across all posted SBAs using specific or strings of keywords.

Speaking to this slide, I believe the integrated review provides an improvement from the discipline-specific reviews. As already emphasized, there's a more concise summary that removes duplicative information that was seen in

the old format. The summary format enables a layperson such as a consumer to better comprehend the information that contributed to the FDA's decision.

Based on these available examples, I was able to find the same types of information one would previously expect to find in the discipline-specific format. Because I will be using these review packages for the same purpose as before, also previously articulated, it still is a bit of an unknown to me whether there is an additional layer of detail that may be excluded; so including negotiations between sponsor and FDA on specific issues or the FDA's refusal of sponsor requests to use specific types of information to contribute to the overall profile safety or efficacy.

Just to quickly wrap up, I wanted to share with you an analysis I did within my group to understand sponsor proposals for the use of real-world data and evidence to support product approval. We were able to find examples of both

FDA acceptance as well as rejection of the sponsor's proposed use. I highlight two of the examples, and using the old format, this one-page review, we were able to extract helpful details that clearly explained the FDA's rationale for refusal, included on the right-hand column.

In closing, transparency is definitely going to improve the predictability. Provided there's only a small sample of the value of the review information available, I expect the information will continue to be valuable to inform my colleagues to understand current agency trends, avoid asking already answered questions, potentially reducing meeting requests, and avoiding past mistakes. This will ultimately benefit the agency, sponsors, and patients. Thanks again for the opportunity and your consideration as you work to continue to refine this process.

DR. HEARNS-STEWART: Thank you very much, Ms. Huddle, for your insightful presentation and for your suggestions. Again, we will be sure to consider your recommendations as we continue to

refine the process and the template.

We'd like to thank everyone for their time and attention during our morning session. We are going to break for lunch, but please rejoin us at 1:15 after the lunch break. Thank you very much.

(Whereupon, at 12:18 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

Panel Discussion

MR. TYBERG: Good afternoon, everybody. It's 1:30. We'd like to begin our second set of sessions, the second session for this workshop today. My name is Yoni Tyberg. I'm the acting team leader for the special programs staff in OND, and our office again oversees and supports the implementation of the New Drugs Regulatory Program Modernization efforts. Our team also provides the program evaluation support across all the newly implemented workstreams, including the integrated assessment of marketing applications.

Today, this next session that we're going to have is going to take us through 1:30 to 2:45. We have a wonderful panel here who's going to provide from many different types of disciplines, from leadership and disciplines as well, who have all engaged in this new process, and they're going to share their experiences.

Earlier throughout the session thus far,

we've spoke about it in theory, and it's really nice to hear from the users, the end users, who have been going through this process and their experiences to learn what their experiences are, some of the challenges as well, some of the learning curves, as well as the rewarding and beneficial experiences that they've been having.

We'd also like to look at some of the future aspirations from the panelists to hear where they see, as we've noted earlier, slowly building up and bringing on more different types of applications as we're rolling this out in a broader sense. We also hope to weave in some of the public questions that have come in. We're going to try our best to weave as much as we can into some of those, and I'll prompt when necessary.

We really, again, thank the panel for coming, and I'm going to introduce them. What's nice is I thought I'd draw the short straw to try to bring everyone back from lunch, but what's nice about being, I guess, in a virtual setting is people can -- not the panel, but panelists can do

that, too, I guess. But the audience can certainly sit and eat, and just listen, and really hear from the panelists.

So I'm going to go ahead and introduce the panelists now in order, and that's Sarah Connelly, who's the acting clinical team leader in the Division of Antivirals in OND's Office of Infectious Diseases with CDER. We have John Farley, who we heard from earlier, the director of OND's Office of Infectious Diseases.

We have Kerry Jo Lee, acting associate director for Rare Diseases in the Office of New Drugs. We have Stephanie Quinn, a pharmacology-toxicology associate director within the Office of New Drug's immediate office. We have Jin Liu who leads OND's clinical data scientists team, who again is that new role that we have, the clinical data scientists who's supporting our clinical team.

We have Jennifer Mercier, the director of the Office of Regulatory Operations in the Office of New Drugs. We have Florence Moore, science policy analyst with the special programs staff in

the Office of New Drugs and serves as the program manager for the integrated assessment of marketing applications. We have Kellie Reynolds, the director of the Division of Infectious Disease Pharmacology in the Office of Clinical Pharmacology.

We have Lisa Skarupa who's the senior regulatory health project manager in the Division of Regulatory Operations for Specialty Medicine, and that's with the Office of Regulatory Operations. We have Kimberly Struble who's the senior clinical analyst team leader in the Division of Antivirals in the Office of Infectious Diseases. We have Aliza Thompson who's the deputy director of the Division of Cardiology and Nephrology, and we have Therri Usher who's the mathematical statistician within CDER.

So again, I want to thank the panel, really a large panel, like I said, from many different disciplines and many different levels of leadership, who have joined us, and who's going to share with us some of their experiences going

through the integrated assessment marketing applications process and using the template itself, so thank you, and I see that you have a list of the different panelists.

What I'm going to do is, again, because we're in a different environment, I'm going to go ahead and state some questions, and maybe some prompts, and maybe select some of the panelists. If you can please, when I call you, just feel free to jump in.

The first question I want to bring up and address, and I'll ask you verbatim, is you all have experienced using the integrated assessment and marketing applications, both the documentation and the process. Have you experienced any challenges adjusting to the new process and template? If so, how did you overcome them or how would you recommend addressing them in the future?

I'm going to pick Stephanie Quinn from pharm-tox, associate director from a pharm-tox perspective. We'd love to hear your perspective.

DR. LEUENROTH-QUINN: Sure. From a

pharm-tox perspective, I think the major issue is whenever you change templates, there's going to be a learning curve. Certainly, it has taken some time to get used to the new template as well as the new process. It's really trying to identify how to now compartmentalize all of the information that we've previously written in these discipline-specific reviews; for example, bringing all of the high-level review issues up front into the integrated assessment and then putting all of that detail back in the pharm-tox specific appendix.

Even within that integrated assessment piece of this new template, there are many different sections where pharm-tox will be writing information; for example, trying to figure out what high-level information needs to go into the benefits section, so any primary pharmacology data that needs to be highlighted there, and then putting in all of the high-level nonclinical toxicity information as well.

I think, also, another challenge has been

how to write with others in the same space. For example, if you have a particular review issue and other disciplines need to weigh in on that, simply from a practical perspective, how you go about writing that section, who's going to lead, what is going to be the progression of that discussion, things like that have been a challenge.

Speaking to the appendix itself, pharm-tox, we have a lot of information that we're trying to review. So the challenge there has been about the amount of detail to place in that and how to put in detail in a meaningful way. We've been trying to look to using tables, for example, to put in some study design detail there, and then really highlighting all of the nonclinical toxicities and rationale and the scientific discussion around that.

But I think overcoming all of this really comes down to training and experience. As has been stated earlier, there's a lot of ongoing training. In addition to that, as more and more reviewers have experience with this template and the process,

we can simply ask our colleagues for advice and any recommendations for this entire process. Thank you.

MR. TYBERG: Great. Thank you. Those are excellent, great points. As I'm doing these evaluations, I know I do hear those adjustments as each team is going through this, so I think what you shared certainly applies all around.

I'd like to call on Kim Struble if she can give her experience as a CDTL, who's sort of the quarterback as the clinical team lead who's really trying bring all this together both from the different disciplines. I'd love to hear your experience.

DR. STRUBLE: Thank you, Yoni.

In the Division of Antivirals, we've actually really embraced the new process. We've implemented review issue-based internal NDA review team meetings over the past several years, especially during the review of complicated hepatitis C applications. But as Stephanie pointed out, really, the new challenge relates to using

this integrated template.

From the cross-discipline team leader perspective, our challenge has been the collaborative writing because, as everyone knows, at FDA, each reviewer produces their own individual discipline-specific review, and now our focus is on this integrated writing and collaborative writing, and it's a bit different and challenging, especially when you have an issue that involves several different review disciplines. Industry is really used to producing one document versus these discipline-specific documents, and we hope to learn more about those best practices as we bring those forward for our reviews as well.

One challenge from the CTL perspective is really how to best efficiently and effectively lead the team so that we adequately can clearly document why we consider something an issue, what was our assessment, and how we came to our conclusion and regulatory decision process, while all preserving equal voice and individual perspectives.

For each review issue, in our division we've

initiated these writing sessions with the reviewers and the team leaders to really align on who was going to be the lead for these review issues, align on the analysis and assessment elements, and the overall organization, so that that review issues section really tells a comprehensive story to support our decisions. From my perspective, this has been very helpful, especially in our new work environment, so thank you.

MR. TYBERG: Thank you for that information.

Kim, I would highlight the intent, like you had indicated, from industry in terms of how they do it. I'll just put a plug like I did earlier. The FRN notice is still open, and I'm sure that will be a great way for us to hear, based on the feedback that we're giving, some tips and certainly some suggestions as well in terms of how best to do that, too. So thank you for sharing that with us, Kim.

Kellie Reynolds, as division director from the Office of Clin-Pharm, I'd love to hear your perspective on some of these issues and your

experience.

DR. REYNOLDS: Sure. Thank you. I'll be happy to share that. First, many of the applications that I have personally been experienced with has been with the same division that Kim works with, so I've had a lot of the same experience as far as how she mentioned, having the collaborative meetings, which is essential if you have multiple reviewers working on the same section of the review.

I've been involved with this process since we started it, and I know that when we started going out and talking about what was going to happen, no one could understand what does collaborative writing really mean, and it's hard to explain until someone's actually been a part of it. So I agree with the collaborative writing sessions where you outline who's going to cover what bullet points.

Also, one thing that helps is if the team comes up with a way that they're going to edit each other's work. You have to work together as a team.

You're going to be commenting on someone else's work because it's in the same paragraph that you're writing, so coming up with ground rules for how you're going to edit each other's work or just provide comments on the side is important.

One thing that specifically affects me is how am I going to provide comments on the reviewer and the team leader that report to me. In the past, they would write their full review. I would see a draft after the team leader has looked at it, and I would provide my comments, and there was a distinct document. So now there's the challenge of, well, how do I provide my tertiary review of a document that 20 people are writing? And many of them don't report to me; some don't even know me.

I think it has really forced me to go to more of the multidisciplinary team meetings where they're discussing the application, so that's good. I have a better idea of the context of the review process and how the whole team is moving towards their decision, so I read through the review more frequently and see how the other disciplines are

starting to populate it. When I'm working with the reviewer and team leader from clin-pharm, it's more discussion based than me writing directly in the review. So in the end, it was a learning curve, but I think we ended up at a better place.

MR. TYBERG: That's great, and I guess that also demonstrates those two aspects of not only is the document more integrated, but the touch points for our teams have been -- it's almost enforced, where we're meeting at -- again, I'll say those JAM sessions, where we have that opportunity to have those discussions, whereas it used to be that maybe those discussions were happening a little bit too later. But now we're incorporating those, so it sounds like we're learning from taking those opportunities to meet with one another, the disciplines, and also leadership level -- so leadership's involved now -- to really get at some of those conversations and having those earlier on.

That's great. Thank you for sharing.

In a similar vein, I guess -- and it's a great segue because, Kellie, you have been in that

process for quite a while, since its inception, as we started rolling this out. Considering what those learning curves are and in terms of what some of you have witnessed and experienced with those learning curves in the earlier phases, and then working its way into where we are in implementation, I guess a similar question, if I could call to Aliza Thompson, who's the deputy director in her division, and some of your early experience, and how it transpired throughout.

DR. THOMPSON: Well, thank you for that question, and hopefully everyone can hear me above the noise in the yard. Our division was one of the early divisions to actually use the template, and I admit it was a bit challenging in the beginning. I think one of the biggest challenges was that, at the same time that you were getting the application, they were also training you, until all of a sudden you had all these training sessions you needed to attend.

I think for the review team, at a time when we were all trying to focus on the application and

get oriented to the application, to have to go to all sorts of training sessions was just incredibly challenging. But we gave feedback about this, and I think that the process has much improved based on that feedback. They now do the training and expect people to be trained before they actually get the applications. Just looking at the training that they've developed over the time period, I think it's much better and much stronger. So yes, it's certainly gotten a lot better.

MR. TYBERG: That's great. Those periods of evaluation -- a cohort, we call them -- as some applications go through, we have the opportunity to apply almost like a -- go in a little bit more with a finer tooth comb with the team to see on many levels what needs to improve, what areas, whether it be a training piece, whether it be some support piece, or a resource piece. That's why it's critical as we're rolling something like this. And that change management piece, we really have that evaluation team to really go in there and see what changes need to be made.

So to your point, I think that's what we're trying to do. We've heard that and, obviously, as you noted, we are actively making those changes around the training front, and the resource front, et cetera.

But talking about resources, we're very lucky to have Jin Liu who is really standing up a new team, a new army of clinical data specialists, a clinical data scientist role. From what we're hearing, again, from the evaluations team perspective, it's been such an amazing add to the team.

Again, Jin, you have been also involved from earlier on when we were designing and developing this and designing your role and your team. I'd love to hear your perspective, how you've been integrating and working with the clinical team and some of the work that you've been doing with that, and how that's been helpful.

DR. LIU: Thank you, Yoni. I hope people can hear me and see me. Great. My name is Jin Liu, and I'm leading the clinical data scientist

team. In the new review process, as Yoni mentioned, my team is supporting the clinical review teams with safety data quality assessments and safety data analysis for NDA and BLA reviews.

From a clinical data scientist perspective, I'd like to share two learning curves that I have experienced. One is about the interactions with the clinical review team, and the other one is about the deliverables provided by my team. First, during the initial phases of the implementation, some clinical review teams didn't know how to interact with the clinical data scientists, when to involve us and what our expertise is.

Because we represent a new discipline, no one really had experience in terms of how to interact our work with each other efficiently. To improve on this, we have been collecting and incorporating the feedback and comments from the clinical review teams, and we also optimized CDER's workflow to make sure it is aligned with the new review process.

Second, during the initial phases of the

implementation, the type of deliverables provided by my team, like safety data quality assessment or safety data analysis, sometimes it contains too much typing details or some useful information needed by the clinical review team. So to improve on this, we have been working with experienced clinical reviewers and also data scientists and data analysts to develop and deliver more feasible purpose deliverables related to safety data analysis.

These deliverables contain comprehensive data analysis results and necessary technical details. I'm very happy that both things have been greatly improved, and my team will continue improving our workflow and deliverables by collecting and incorporating the feedback from the clinical review teams.

Thank you, Yoni.

MR. TYBERG: Thank you, Jin. That's great to hear.

In terms of my component, I've certainly been with you earlier on when we were just piloting

this, and just the growth of your team and, I think, the work and the compliments we get for the work that you all do, I can't say that enough. So publicly, I want to say that people do enjoy -- we really appreciate the work and the type of work that you add to the review team. So thank you for that overview of the level of work you're doing and the support you're giving to our team. It's nice to hear as it's progressing.

I'm going to shift now to talk a little bit more about the benefits that some of our review teams are seeing, and I'll pose a question, and then I'll reach out to the row of our panelists. I'll just state the question.

In what ways has working with the integrated assessment process, again process and the template, been rewarding and beneficial thus far? I'm going to call on Therri, if you can give us your perspective. From the biostat's perspective, what has been what you've been seeing as rewarding and beneficial in this new process and template?

DR. USHER: Thank you for posing this

question. There have been several benefits working with the new template. The first I would have to say is increased communication and collaboration with review colleagues.

A lot of my work with the new integrated template has been in relation to the Division of Antivirals, which already had a strong culture of collaboration and communication between disciplines, however, the new integrated template took it to the next level. There were thoughtful communications and thoughtful discussions throughout the review process with regards to review issues, writing, and so on.

Also, I've appreciated the change in the focus from documenting the review process to outlining the review thought process. This transition I think hasn't received enough credit. Oftentimes as a reviewer, we think of the review as a documentation of the review, but really what it's supposed to do, and as several stakeholders have mentioned today, is it's supposed to give stakeholders a clear idea of the agency's thought

process and what led us to the decision that was made regarding approval and so on. So the new template has just illuminated our thought process and kind of changed our focus and our thought of what a review should actually do.

While there has been less writing -- for instance, as a reviewer, I no longer have to explain regulatory history because that part is already given in the integrated assessment by another one of my colleagues -- the writing that's done is now more intentional, and that's because we have more time to think critically rather than writing out details that are already given in multiple other reviews.

So with this additional time to think critically, we really come to a better understanding of what the review issue is and what the key components are that we wish to convey to stakeholders. So I'll stop there.

MR. TYBERG: Great. Thank you for that. I know we touched on that earlier. There's a separate section within the document, within the

integrated review document, full document, and sitting in there is that regulatory history that now is authored, I believe, in conjunction with your other colleagues. But I think that provides the ability to, like you said, focus in and worry more on the stats piece, and working with your clinical colleagues, and to be less worried about just going through that history. Obviously, we do those cross-checks for sure, but as you noted, there's a great save there in terms of time and effort and more focus.

Florence, if you're with us, I'd love to hear. I'll just introduce you. You, again, have been here earlier on and have helped develop this process from the start from the special programs staff. As a program manager of this whole huge initiative, you've seen it from your perspective. We'd love to hear what you've seen rewarding and beneficial thus far because you see it from all the teams that are going through this. You're hearing from everybody. You're like that nexus, so I'd love to hear your perspective.

DR. MOORE: Thank you, Yoni. Actually, I'm going to speak from the perspective of my former role as well. As one who used to use NDA and BLA review documents to help determine often exclusivity determination, and also as a member of the implementation team helping to collate this effort, I have heard from review teams in implementation that the new integrated review template is more streamlined.

In addition, it provides a more easy way to identify information within the document. For example, it's easier to find the rationale for the decision made. One good thing that I've heard also, a beneficial aspect that I've heard from the review team, is because it is review issue based and focusing on all disciplines' perspective, which includes both the core disciplines as well as the subject matter experts, it helps reduce redundancy. I think we heard that a lot this morning from our external panelists as well.

One key aspect of the process, as was noted earlier, is the involvement of leadership. I've

heard the reviewers appreciating that aspect because it allows for the leadership to provide more guidance earlier in the process and alignments, and it avoids any surprises that may come up later on in the review cycle.

Lastly but not least, one thing that I think we've heard many, many times through the discussion today is that the process allows for a collaborative nature or collaborative approach, which enhances more transparency and also allows our reviewers to do more critical thinking compared to the previous unit review or the clinical template that we used. Thank you.

MR. TYBERG: Great. Thank you, Florence.

Yes, we've heard time and time again -- again, going back to those JAM sessions of incorporating leadership earlier on from that benefit-risk early on in the review now, and those JAM sessions having and incorporating the leadership in there, has had some great beneficial effects on, really, guidance and decision making.

I'm going to turn to Lisa Skarupa, who is

one of the RPMs with us. Lisa, yep, I see you. I'd love to hear your perspective. I know you've been through the gauntlet of the integrated assessment and the change management, and I'd love to hear your perspectives.

MS. SKARUPA: Thank you, Yoni.

I'm Lisa Skarupa. Thank you for allowing me to be here at the panel. I work with several of the project managers during this implementation, so I do want to take the time to shout out to those who have been excellent and dedicated in helping this initiative, and who will be participating in the future.

From a regulatory project manager's perspective, what I hear -- and this goes back to what we do, and that is not just coordinate internal meetings and communicate with the external stakeholders, but also to help the team get through the timeline and provide the deliverables. In that process, the project managers have learned to hear are there ways to communicate to the leaders to voice the needs and what they are concerned about,

and how do you get this information and resources?

Earlier today, you've heard all the different resources listed. This integrated assessment initiative was designed to have the various ways to provide relevant information and the resources to resolve those challenges, including the comprehensive templates. This was all components that were placed in a centralized location, and that alleviated much of the stress for the project managers in explaining and providing this information to the review team.

I won't get into the details of the SharePoint because that was Dr. Hearns-Stewart's talk, but it has been a tremendous help. Providing those best practice tips and examples of the end products helped me to help the reviewers get through this process, so I'm impressed with the massive efforts in presenting this information in a variety of methods when reaching out to the large audience of the Office of New Drugs. Yet, knowing that each of us, including reviewers, are different in the way we learn and in our learning pace,

having the implementation team in our meetings helped a lot with the review team who had concerns, and they were right there to answer the questions in real time.

The role as a project manager can be difficult when you meet a new review team that becomes resistant to the process. For the few that request to change meant letting go of their methods that has been accepted over a very long period of time, so aid from the team leaders and the division directors were needed to interpret the barriers and to help clarify the goals. So once again, the flow and the implementation team were there to meet with us and get answers for the review team.

Another observation that I've seen is that there's a difference in outcomes and adapting, the degree of adaptation, when the implementation is done gradually in phases. Starting with divisions, before adding more divisions, this allowed the time, as brought up in earlier topics, to hear the feedback, to synthesize, and then respond to each division.

During this initial year, I've heard individuals were able to share their personal experiences and to realize that they are contributing to tailoring the elements of this new process. With the significant shift for the reviewers to do more collaboration, all the resources were necessary in order for the review team to accomplish the desired goal. So achieving these goals meant they had to build new collaborations, and that success for the team now depended on each member having to actively work with each other, so thank you.

I do want to jump off and mention the addition of the medical editors in the review process because they affected our roles as well. It alleviated those few PMs who did the formatting back in the olden days, but I know a lot of the CDTLs did that as well. That was an enormous amount of help and alleviated us to do more things for the regulatory aspects of our job. Thank you.

MR. TYBERG: Thank you, Lisa. I know our change management strategy is working when I hear

you say "in the olden days," so that's good. Yes, and I cannot echo that that's something that we've heard time and time again, is our medical editors, which we need to give them kudos and applause for what they do to help make the document look the way it does when it comes out, so thank you. Thank you for bringing that up. That's an excellent point.

I'm going to skip now to Jennifer Mercier, the director of ORO. It's a relatively new office; well, it's a new restructured office. But from the director's perspective from a regulatory office, I'd love to hear your perspective. And I know you've been involved in the design and have seen the program go along its way, so I'd love to hear your perspective.

MS. MERCIER: Thank you for having me here, first of all. I would like to echo some of the items that Lisa brought up as a regulatory project manager or former regulatory project manager. One of the things that I think has been a very big step for our group is the fact that we are now writing the regulatory history in the document, so we're

part of the actual review staff and the review team.

I know we've always felt like we were part of the review team, but our roles have changed a little bit, which is a very nice item to help elevate our project management staff within OND. We have a lot of really, really smart people. This is what our job is, so I really applauded that part of the review template.

One of the other things that I think is very helpful for project managers is the identification of review issues early on and engaging the leadership ahead of time. This helps us plan who we need to get involved early on. The review staff changes. We need to consult other areas. So that is very, very beneficial for us for time saving and efficiency purposes.

One of the other items that I think this document helps with is keeping our processes very similar across the divisions. It helps give us a little bit more transparency into how we do things. But I echo a lot of the items that everybody else

has already spoke about, and the medical editors, thank you so much for them. As a project manager who did do a lot of editing with documents, whether it was the individual review and someone didn't know how to do something, we appreciate them so much, so thank you.

MR. TYBERG: Thank you for echoing that as well. Coming from your perspective and from your experience, yes, it's coming more from you than from me for sure. So thank you for the noting that.

Kim, if you can give us some of your perspective, again, from the CDTL's perspective in terms of what you've been seeing. I think you've gone through the process a number of times, and I can't count how many; I'm not sure. But I'd love to hear your perspective of some of the benefits that you've been seeing from your team and just the outputs.

DR. STRUBLE: Great. Thank you, Yoni. Yes, I've been through this six times already, including the first table-top exercise that we did to develop

the process.

I should have mentioned that one of the challenges at the beginning was that going first sometimes is really hard because you don't have precedent, and you're making stuff up, and you don't know if you're doing it efficiently, and you don't want to draw from others. So it's great that we have other examples and we can support each other.

Some of the benefits, like others said, having Jin's group, and the CDS, and the medical editors has significantly helped the review team. Now when I do applications where I don't have that support, I'm spoiled. It's kind of hard to go back the other way.

Also, I do like having the review issues identified. Particularly if you have a team that's been on an application from the very beginning, you identify those issues throughout drug development. As this is part of the process, you have your review issues at the pre-NDA meeting, so the team, when they get the application, they're looking for

these key issues.

The benefit is having these review issues up front as we center all our JAM meetings around these review issues. We have integrated reviews with all the disciplines. We just don't stop there. It's like, well, how does this review issue impact labeling? So we can talk about labeling much sooner in the review process. How does this impact PMRs or PMCs? So those get talked about early in the process as well or is there additional safety monitoring and pharmacovigilance that's going to be needed. So a lot of those things are talked about so much earlier.

It's great having senior management leadership at all these key meetings. They were at many milestone meetings in the past but more engaged and knowing the review issues. So we can get their input earlier, and it really benefits the review team to start that collaborative writing process as opposed to having waiting to the very end to try to figure out where we stand on things and aligning our organization of those thoughts,

too.

So there's been great benefits. I think the one that resonates best with me is the review issue section, and it's clearly outlined. In the past, we've looked at the individual reviews and they refer to everybody's review, but the whole issue was maybe not completely closed out or you didn't know where the resolution was. Now I think it's much more clear and transparent, so thank you.

MR. TYBERG: Great. Thank you for that. I didn't realize it was six. Wow. I didn't realize it was that much, so that's great. Thanks for that input.

I want to shift, and I'll pose the question. I'll go down the line to many of you.

Thinking about given your experience now -- and some more than others -- working in the integrated assessment process and using the documents, thinking futuristic, what would you like to see more of and less of moving forward? What are those items? Some of it you've shared. I can imagine that there's some things that you would

want increase of. It could be support. I don't want to lead you anywhere, but I'd love to hear your thoughts, and we can certainly go down the line here.

I guess I'll call on Stephanie from pharm-tox, from your perspective, I'd love to hear your thoughts looking in the future.

DR. LEUENROTH-QUINN: From my point of view, I think expanding the template to other types of marketing applications is something that I would definitely like to see, and I say that for two reasons. One is that I think the integrated review template has extreme value to tell that story from a high-level perspective, as well as retaining all of that detailed information in the appendices, I think is very valuable.

Then, if we expanded the use of this template in the future, again, as I talked about before, having one template that everyone is comfortable with, I think that is what the preference may be, rather than switching gears between one template and another. I think that

becomes more difficult. So having perhaps the integrated template for all marketing applications in the future would be beneficial. However, with that said, I think there's also the opportunity there for some amount of flexibility. For example, if there were new sections, kind of like a modular appendix for these different types of applications, perhaps that's a way to go as well.

In terms of the process moving forward, I think there is always the opportunity to tweak things a bit. Those are discussions that we continue to have in order to try to make this process and the template as best as possible. Also, as everyone else has said, I would certainly love to see the medical editor role continue because from a scientific perspective, you want to have time to think about the issues and write the review and not worry about is the font change different or is the table numbering different. So knowing that someone is there to take care of that aspect I think is a really big help. So I'll stop there.

MR. TYBERG: Thank you. Yes, we're no good at taking notes on that for sure. Thank you for that, Stephanie.

I'll pose the same question to Therri. From a biostat's perspective, looking forward, what would you like to see more of and less of?

DR. USHER: Thanks, Yoni.

I would like to second what Stephanie said about the expansion of the scope of the review. My first experience with the new template was as a reviewer supporting the Division of Antivirals. I'm now a reviewer that supports the Division of Rare Diseases and Medical Genetics. One thing about rare disease marketing applications, they all look uniquely different, so it's very important that we have a template that can be utilized for all of these different marketing applications that we see.

I would also like to see a break from the traditional discipline-specific thinking. For instance, Dr. Farley mentioned earlier how important clinicians are in assessing benefit.

They provide us with an understanding of a clinical benefit. That's a break from the traditional thinking that statistics focus on efficacy while clinical focuses on safety.

This new process and template promotes interdisciplinary review and interdisciplinary thinking across all the different aspects of the benefit-risk framework, and it has a fundamental stance that disciplines can contribute to multiple areas of a review, and all disciplines should contribute to the assessment of benefit-risk.

Finally, I would like to see more communication between the FDA and applicants submitting marketing applications about what is needed for the new template, such as providing protocol synopses or visuals that can be utilized within the template. Thank you.

MR. TYBERG: Great. Thank you. I love that point about, in a way, the document itself allows for -- it almost enhances that equal voice on issues from all disciplines, so thank you for that point. And just to flag your point about we'd love

to hear more from our stakeholders and what they want to see, obviously. It's still open. Just another infomercial for that, it's through December, and we look forward to looking at some of those comments from there following this meeting.

I'll pose the same question, the same thing, thinking about the future with the integrated assessment. Lisa Skarupa, from an RPM's perspective, I'd love to hear from you, your vision.

MS. SKARUPA: Hi, Yoni. Thank you.

I think, once again, resources. As we expand to more divisions, there are going to be more questions and more anxiety on what to do with these templates, how to get through to the timeline, and having to do meetings earlier. There are just a lot of factors that the project manager has to deal with during those meetings, so I'd like to see that they continue synthesizing the feedback and expanding the SharePoint site for resources.

I think when we hear the successes of a completed integrated review and celebrating that, I

think that visibility of those small successes help other teams and the team themselves to build confidence and to be able to do that again in the other subsequent integrated reviews. So I think that's going to help as we celebrate little successes after we complete each integrated review. Thank you.

MR. TYBERG: Thank you for that. We'll be sure to pass the good news on to other divisions who are just getting into it and scaling up.

Kim Struble, if you could talk to that point. As you move on maybe to your seventh or eighth --

DR. STRUBLE: I have.

MR. TYBERG: -- in your mind, thinking for the future as a veteran, what would you like to see more of and less of?

DR. STRUBLE: I think I'd just echo what everyone else says. Making sure that we have that support available for medical editors in the CDS team for all these applications I think is critical, too. We've done in our division -- I've

done a couple NMEs, a new fixed dose of already approved products and efficacy supplements. What we haven't really done is a large scale scope of these efficacy supplements.

I think that the pediatric supplements could really benefit from this because there are very complicated antivirals, some pharmacokinetic and clinical and safety information. Particularly when you go to certain weight bands, you have higher exposures and do you have enough safety to support that. They're across two different reviews and could definitely benefit from an integrated review so it's very easy for the outside to understand why we made certain dosing recommendations.

Another thing our division does is medical countermeasures and applications based on the Animal Rule. Right now, the current template would not necessarily fit like an Animal Rule type review process, but something that we could look toward the future to how we could adapt that to look at those Animal Rule type applications, so thank you.

MR. TYBERG: Great. No, thank you. To your

earlier point, I think one thing we emphasize with the template is that knowledge management aspect. The hope is that we will be able to easily extract out some of those questions that may be similar or that we set precedent from in other reviews so we can provide consistency and answers. The document itself and the ability to have that knowledge management aspect of it will only help enforce that and help us get to that piece, so thank you.

Kellie Reynolds, from a clin-pharm perspective, I'd love to hear your perspective looking in the future.

DR. REYNOLDS: I definitely agree with Kim regarding the pediatric supplements being a good place to go next because often it is challenging. Which review does this information go in? Does it go in clinical? Does it go in clinical pharmacology? Does it go in pharmacometrics? And the answer is, all of them. So it would be nice to have all of that information integrated together.

There are two areas where I think that sharing examples would be helpful. One, in

addition, once we finish a nice integrated review and celebrating the success, communicate how we got there because the conversations we have are challenging but rewarding when we resolve them. I know there's at least one application that I've worked on with Kim where we had a lot of discussion around what are the key review issues. There were disagreements about, well, this is an issue, and we're looking at it, and it's something we're addressing, and is it really a key review issue?

For me, that was a very educational process because it changed my perspective of what a key review issue was because you wouldn't know that from looking at the review. You just see the final product of what we identified as a key review issue. So I think communicating those lessons learned would be really valuable to other review teams.

The other area would be sharing examples of how disagreements are documented, and this came up in a lot of the stakeholder comments earlier on. You're sharing those examples within FDA, but then

also you're sharing them with the stakeholders and seeing if the message that we're sending to them is actually the message that we intended to send. We want to communicate what were the multiple points of view, we want to communicate how we resolved it, but we don't want unintended consequences. I think one of the stakeholders mentioned that also. So I think that's a really important area for us to start discussing.

MR. TYBERG: That's important, your point about the feedback to the team. Certainly that was a great lesson learned and something I think -- I'm taking a note down, from an evaluator's perspective, of how best to incorporate that feedback to teams to learn how you handle, in your example, those disagreements.

Again, you're just exemplifying that this process does allow and show the ability to have those conversations. And the fact that you, as you stated, are learning from those is just, again, a testament to how having these new meetings and the new collaboration can help each other learn an

issue, how to document those issues, and certainly for us to take notes of how best to continue that type of learning within all the teams as they're staffing up this type of effort.

I'll pose the question just going down the line here. Jennifer Mercier, as the director of the ORO from the regulatory office, I'd love to hear your input and what you see down the road in terms of the future; what you'd like to see more of and less of.

MS. MERCIER: Well, I like the topics that everybody has already mentioned. I think I'm in agreement with most of those as well. I like the idea of having this be more of a working document -- and we've been refining it -- and not just the document itself but the processes, and the training, and the things that go around it, which as anybody who's been here for any length of time knows that's not traditionally how we have these review templates designed, which will help to make them more consistent in my opinion. If we keep refining it, and we're able to address issues that

we're seeing, that will help with our documents to the public.

I think that one of the items, which I wasn't aware of until today, was people having an issue with searchability within our documents. I think that maybe some newer technologies and platforms that we're using could maybe help with aiding the public to be able to search our documents. Those are things that we need to take back, look back on, and see how we can better handle those processes, and I don't know the answer to that yet. I don't think I will get it; I think it would be Nancy.

It's nice to be on a team to develop these items, hear the feedback we're getting, and really work with this group to come up with solutions. I think that's only going to help. Obviously, in our virtual world right now, we're learning a lot more about how we can refine things and be more efficient in how we're doing our work. So I'd like to see more of that happen. I don't know how long we're going to be in virtual, so we need to use our

technologies that we have available to do that.

MR. TYBERG: Absolutely. Yes, it's definitely an adjustment. When we talk about change management of getting used to this, looking at everyone around a screen, that's definitely an adjustment. But thank you for those comments.

If I can call on, I think, Jin. I'm sorry. Aliza Thompson -- I'm sorry -- I'd love to hear from your perspective, looking as a division director, what you see in the future as this process rolls out, some of the things that you would like to have more of, potentially less of.

DR. THOMPSON: Great. I'm actually a deputy. I'm not a division director yet. But I think you're hitting actually a key issue, at least as it relates to one aspect of my job, which is, unfortunately, we are always incredibly short staff, certainly in terms of the clinical staff medical officers. So we're always having to ask ourselves how we can do things more effectively and more efficiently. I think that's been one of the great appeals of this integrated review, to avoid

the redundancy, the redundancy between disciplines as well as the redundancy as you go up the ladder in terms of the different levels of review.

This has been an incredibly attractive program for us, and I think the greatest barrier at this point for us has been that you can't accept more applications into the program because of resource constraints and also just the types of applications that you've limited the program to at this point; in addition to -- I think people raised the issue -- obviously the pediatric applications. We get a lot of efficacy supplements, and they're important efficacy supplements, but it would be great if we could get those into the program.

I just also want to give a shout out as well to the medical editors and also the CDS. It's tremendously helpful to have this as an additional resource, again, just bearing in mind how short-staffed we are.

MR. TYBERG: Yes, thank you. As we think about technology, we're hoping that we are building in efficiencies with some of the technology as we

start incorporating them into the review process based on some of the workflows and some of the interfaces we intend to use and bring in the document. So the hope is that it will also help, we hope, free up at least some level of burden so, again, reviewers can be more focused on doing the scientific work and less of the process work.

I'd like to direct a question to Jin. I'm sorry, Jin. I meant to call on you earlier, but that's fine. But Jin, I'd love to hear from your perspective, from the CDS, that new role, in terms of your role as it expands, what do you see for the future in terms of some of the things as we roll this out?

DR. LIU: Thank you, Yoni.

I'd like to share two thoughts. First, I really want to see more collaborations between the clinical review team and the clinical data scientists because the CDS team really wants to hear more feedback and comments and needs from the clinical review team to help us improve our workflow and deliverables.

For example, we worked with Kim's team and Aliza's division several times. For each time, we can learn something new and obtain some valuable feedback and comments from them, which is greatly helpful to our workflow and deliverables. This is going to be the best way for my team to further improve the workflow and deliverables.

The second thing is, as we mentioned several times in today's discussion, we are still in the process of building the clinical data scientist team. I guess it's the same thing for the medical editor team. So I want to see more work and support to ensure that we will have enough clinical data scientist staff to cover all the workload. Yes, I think that's it. Thank you.

MR. TYBERG: Thank you. Thanks for that comment.

If I can call Kerry Jo. Kerry Jo, you again have been around the block with this program from the start and you've seen it from inception, so I'd love to hear your thoughts on the future as we roll this out.

DR. LEE: Thanks. First of all, I'd just like to thank everyone, both our internal and external stakeholders, for participating in this today and being so open. I found it really informative. I think that my thoughts for the future, particularly after hearing people today, are we focused a lot today on the newer elements of the integrated assessment that people weren't familiar with or were concerned about, whether that was interdisciplinary collaboration and documentation or whether that was clarity surrounding how we might capture disagreement.

But I think what we've heard from, particularly external stakeholders, is to really ensure that they can still find what we would consider the critical elements of scientific and regulatory review. So whether that's a primary endpoint change at whatever point during the life cycle of drug development and why, and whether that's the acceptability, or not, of a PRO model and why. These are elements that no matter what type of review template we're writing in, we would

ensure are contained.

I think an opportunity here for the integrated assessment as we move forward is to go back, look internally, and really ensure that we are standardizing various types of information to be reported in certain locations that we always know where to go to find it. People don't have to text search to find various critical elements. So I think that that's really a goal that we can go forward and move on in order of meeting our goals of improving both the clarity and the transparency of our regulatory reviews.

MR. TYBERG: Thank you for that. Thank you, Kerry Jo.

Finally, Dr. Farley, John, how are you? Thank you. I'm glad you're able to join us.

In terms of thinking futuristically in terms of this process, you've actually been at the helm of pushing this forward. If it's possible, as you answer the question, I figured I'd weave in a question we've got. We promised we'll try to weave in some of the questions, which I think some may

have been answered already in our panel, as it relates to advisory committees, their feedback, related feedback, related to the issues within integrated assessment, and how is that all going to be integrated?

I'd love to hear your thoughts on that, as well as from an office director's level where you see our program going.

DR. FARLEY: Thanks very much, Yoni.

I think I'll start with what I'm really looking forward to, which is, as I think may have been shared, there are multiple facets to assessing this work product. What we've just started is what I call an internal assessment by the mavens. What that means is basically asking CDER and OND's leadership -- Bob Temple, Peter Stein, Ellis Unger, Julie Beitz, Mary Thanh Hai -- those folks who've been with us a long time and provide direction. I think we want to ask them to really look at the issue of balance.

There's the need to layer information and the need to streamline and make a readable

document, but then it's also important, as we've heard from many of our external stakeholders today, to make sure that we have a complete scientific review; that we're not kind of losing our scientific completeness and quality in this process, and that's very important to everyone in OND.

So that process is starting now, and I'm looking forward to those results. I think this is going to be an ongoing effort, and work, and attention on our part, and certainly will bring up some training needs as well that we'll implement.

I think one of the visions we always had for this document was maybe this could help with AC preparation. We haven't actualized that yet, but I think it's totally possible that, really, you should be structuring your AC around some key review issues that you have, otherwise why are you holding one? So I think we'd like to work on that further. I think, as you may know, OND is also working to support our staff on preparation for advisory committees and coming up with

standardizing the way we do background packages, et cetera. So this review template may very well fit in there.

I think the third thing, as folks have also brought up today, is the issue of expansion. We've done this process and template with some efficacy supplements with new clinical data supporting a new indication, but what about moving onto our efficacy supplements? I think, as Aliza mentioned, once the teams start using it, they generally like it and they don't like going back. The process itself is really very attractive to everyone in terms of really getting the issues on the table, and that also applies to supplements. So I'll stop there, but those are my thoughts.

MR. TYBERG: Great. I appreciate that. Thank you very much, John, for getting that question in. And yes, we are currently working -- as you indicated, OND is working -- we have a separate workstream that's looking at AC meetings and how best internally to incorporate some of the work that we're doing in the review

because it is part of that cycle, and how to incorporate from the integrated review aspects of that; so more to come on that down the road. Thank you very much, John, for your comments.

I do see Sarah has joined us, and I skipped over her. I thought you weren't in, but now you're there, so that's great. You're not escaping this one. But again, as one of the earlier designers of this process, I definitely wanted to hear from you as you're thinking futuristically and what are some of the things that are on your mind.

DR. CONNELLY: Yes. Apologies to everyone who's listening that I was temporarily pulled away. It has been wonderful to work with this group, wonderful to be part of this effort, and wonderful to hear all the feedback from all of our external stakeholders and partners today.

As noted by my colleagues' comments and experiences after going through these initial reviews, I think they've highlighted aspects of identification and communication of review issues, involvement of leadership, along with incorporation

of the clinical data scientists and medical editors as being really valuable as part of the process.

I think moving forward, what we've heard and have a continued focus on is supporting all of us on the review team -- I'm also now going to be one of the CDTLs moving forward -- to enhance effective collaborative writing approaches that preserve transparency and value differences in scientific opinion, being mindful that one of the original integrated review guiding principles is maximizing reviewer time spent on critical thinking to utilize the expertise that all of us have and bring to the application review.

Therefore, just having a continued eye out moving forward for aspects that aren't aligned with this principle, such as opportunities to continue to streamline potential IT challenges, and then further strengthening ways to utilize and leverage knowledge management throughout the entire drug development lifecycle, from premarket to postmarket development because it's all interrelated.

I apologize if I restated some things that

others said, but those are some points I just wanted to make sure were communicated. Thanks.

MR. TYBERG: Thank you.

I'm looking at the time. I think we do have a little more time left, and I do want to try and incorporate potentially one question that came in.

Jin, I don't mean to call you on the spot here, but there's a question that came in, if you can describe maybe in 1 or 2 minutes the role of the clinical data scientist. I know we may have discussed that earlier on in the program in the morning session, but I think it's worth just mentioning it because, like I said, I think people are very interested in knowing that new role.

Go ahead. You have your 1 to 2 minutes to describe that for us.

DR. LIU: Sure. Thank you, Yoni.

The goal of the clinical data scientist with the team is really trying to reduce the workload of the clinical review team and also improve the quality and efficiency of the clinical review. Specifically, what we have been doing is we are

aligning with the clinical reviewers and team leaders and being responsible for executing the safety data analysis plan and provide both types of reports.

The first type of report is trying to evaluate the safety data's sufficiency, integrity, and the quality. The second report is a document containing all the safety tables and the figures. Some of the figures and tables will be needed and incorporated into the review template, and some of the analysis will be requested by the clinical review team to help better evaluate the safety signals.

The third part of what we have been doing is we are trying to verify all the key safety data in the clinical study report analysis and we try to verify all the safety data in the drug label. Last but not least, it's more important for us to be part of the review team and supporting the clinical reviewer and team leader with in-depth and exploratory analysis for specific safety signals.

I guess that's the overview or overall

introduction for the CDS program.

MR. TYBERG: Thank you. And sorry; I didn't mean to call you on the spot there, but you seemed like you answered very comprehensively that question. I can definitely speak for the teams that we very much appreciate your new role and your team that you're building.

I'm looking at the time. I think this brings this session to an end. I do, again, want to thank all the panelists for taking a little bit over an hour of their time with us today to really give us, again, what's really going on in the field as we're rolling this out. It's really from an evaluation perspective.

It's so nice to hear, really, the intimate experiences that you all are experiencing and the collaboration that's occurring. And again, I'll stress that we do intend to, again from an evaluator, really take the comments that you share with us as we come around to your teams and also incorporate what we're hearing from our public stakeholders, which is very important to us, and to

incorporate that into our evaluation machine, and then certainly make sure that our program continues as we start rolling this out across the agency, across OND. So thank you all again, and I appreciate your time and sharing your experiences.

I'm now going to turn it over to Kevin Bugin, who's going to wrap it up.

Wrap-Up and Next Steps

DR. BUGIN: Thank you, Yoni.

Hi, everyone. I'm Kevin Bugin. I am the director of special programs in the Office of New Drugs, but also the lead for the New Drugs Regulatory Program Modernization. It's my great pleasure to wrap us up and give you a quick recap so that if you're like me and you tend to get pulled into each one of the sessions, you forgot about what was discussed in the morning, and this final presentation will hopefully give you something to leave with and refer to. I also want to talk about what's next, and this is really just the beginning. As I think you've heard today, we have a lot of work to do, and we'll continue to

move this forward with the implementation.

First of all, I think today was a huge success, and I hope you all would agree. The way we're measuring success is, as someone mentioned, everyone was very open and we got a lot of great feedback from you all. This is what matters, and this is why success was in large part thanks to all of you. So thank you for joining us today.

Thank you for providing feedback; being on panels; submitting presentations; asking questions in the chat; and sharing comments in the docket and the previous docket from last year. We really do treasure the feedback, try to consider it, and use it as we move forward. And of course, thank you to all of the workshop organizers and the members of the workstream who have made this day possible and have made the integrated assessment of marketing applications possible.

Now quickly to recap, in the beginning of the day, we started with a welcome and introduction to the modernization. The modernization's goal is really to build on past successes and strengths by

implementing problem-focused, interdisciplinary, team-based approaches. We had six core strategic objectives that we set out with in order to do this. That was scientific leadership; integrated assessment; benefit-risk monitoring; managing talent; operational excellence; and knowledge management. The integrated assessment initiative is really the intersection of multiple strategic objectives, and I think one of the real centerpieces of the New Drugs Regulatory Program Modernization.

Now, what was the rationale for designing this program? Well, the new integrated assessment approach really starts with early identification of key issues and focuses on three guiding principles: enhanced communication, interdisciplinary collaboration, and issue-based reviews.

The template is a three-part document. It consists of an executive summary, and interdisciplinary assessment, and appendices. The integrated assessment, we believe and we really have tried to put this in by design, retains

scientific differences of opinion and equal voice throughout both process, interdisciplinary meetings, and the template documentation of scientific differences of opinion. These will reside in the executive summary. You'll see them in the review issue sections of the interdisciplinary assessment and the appendices when necessary.

The action package, which we heard discussed and we saw some of this in the comments that were submitted prior to the meeting, is a separate initiative from the integrated review. While the integrated review document does contain items that overlap with the streamline action package, they are quite distinct and different. However, as we heard today in some of the panels -- and I'll mention this at the end -- there are things that we can do to try to address some of those barriers or challenges to accessing information due to the changes in the action package or the streamlined action package.

Now, recapping on implementation, there have

been 17 divisions that have been introduced to the integrated assessment for new molecular entities and biologic licensing applications, with the goal of continuing to expand the scope of the marketing application over time to additional divisions and also to additional types of applications, so supplements for, say, new indications or expanded indications.

Phased implementation has really allowed an iterative approach through evaluation, gathering feedback like we're doing today, but also from the staff and responsive refinement of the process and template. This is really, we think, a continuous process that who knows if it will ever end. We hope to just continue it, and learn, and improve.

The internal assessment, also, of the completed integrated reviews to date is ongoing. As you just heard from Dr. Farley, we're really looking internally now to ensure these changes that we have made have retained all the best parts of our reviews and added those new parts that were by intent, and once we have that, we hope to continue

to get additional feedback from our external stakeholders as well.

Now, with regards to the external feedback, we heard a synthesis of some of the information that has been submitted to previous dockets and that was submitted to the docket for this workshop, and we had a couple of emerging things that were reviewed.

First of all, just as a recap, the FDA requested those public comments on the integrated review template in 2019. And I'll mention that in 2019 it was a little confusing because at the time, we were very early in this process, and what was shared was sort of that output of what we called the "table top." So we took a previously completed multidisciplinary review of doravirine, a Unireview actually, and used that to then inform the creation of an integrated review.

It's not a perfect scenario, and it didn't benefit from the process of how it would normally have been created, and a couple of other caveats which were mentioned earlier today. But even so,

we received a lot of great feedback, and then of course leading up to this workshop, we've gathered some feedback as well. We'll try to pull that together and we'll try to continue to address that going forward.

Then respondents, it was very clear. I've included a very wide swath of stakeholders, scientists, academics, industry, patient advocacy groups, and individuals. I'd add professional societies and clinicians that are trying to develop guidelines, and the lists would I'm sure go on and on. We've actively worked to address that feedback, and we'll continue to try and do so and monitor the concerns and the benefits expressed by all of our stakeholders as we move forward.

Moving into the panels, which I found my favorite part of the day. We heard that FDA reviews are really used extensively by a very diverse set of stakeholders as I just mentioned. As far as the benefits go, we heard it provides a very clear rationale for the regulatory decisions and it helps to communicate the key review issues

that were identified during the application review.

I also heard it helps to do this in the context of the regulatory framework that we have for making decisions, which is the benefit-risk assessment framework, which I believe is a really helpful thing for communicating those decisions. And it represents an opportunity to make information more available and accessible, and of course that's where some of the key recommendations that we heard from our external stakeholder panelists this morning come into play.

We heard that you really want the inclusion of information regarding the development program, particularly those early development programs issues which may or may not have been resolved prior to the application coming in and are still important to understand. We also have to recognize that these documents will be redacted and that, as I mentioned earlier, the streamline action package is changing what information is immediately available. So if we can, we should try to address those types of information losses in our integrated

review as well.

We also heard about transparency on disagreements and independence for reviewers to document their assessments; so recognizing that we have moved to a collaboratively written document. Also, there's a much more collaborative and heavily interdisciplinary process where many disagreements will be, just frankly, discussed earlier in the process and might be resolved before we get into writing that final information into the document. We do need to find other ways to be transparent about that process.

We also heard that it's very important to include the patient's perspective and experience data in the document and make it more noteworthy how this was considered in the benefit-risk assessment. I think this is a really important piece, and there have been initiatives over the years to improve how we talk about patient experience data, including structuring it with tables, and I think we just need to continue to push on that and add additional information into

our review documents about how we consider it.

We also heard that we need to further incorporate information pertaining to exclusivity, review designations, and other details that can be useful to inform clinical practice. So there are sort of two parts here. One was give me all of that great regulatory information. If I'm a regulatory affairs or intelligence person, that's the golden stuff that I'm looking for. I want to use that as precedents potentially. I want to use that to inform new development plans, et cetera.

Then if I'm a clinician or I'm a member of a committee or a working group that's tasked with writing clinical practice guidelines, I really want to understand all of those details about the safety and the efficacy so I can use that to make decisions about clinical practice guidelines.

Lastly, this was unfortunately something that we heard today, but I think it is good that we heard about it, and I think it is addressable, and we'll certainly work on this going forward, which was to facilitate the accessibility of information

to researchers and patients; so doing things to improve the document navigation such as adding hyperlinks and really testing those hyperlinks.

I think we also have to be cognizant that after the document is checked in, that it moves in a process through redactions and then posting to the Web, and all those hyperlinks are maintained through that process. I also heard that it was very important to ensure the methodological approaches that are used by our review staff and how they analyze and came to their decisions or conducted their assessments. It's really important. It helps those analyses to be recreated by external researchers trying to validate the FDA findings.

Lastly, of course, the information needs to be as patient friendly or in plain language as much as possible. I even heard an early great idea which I think we'll have to truly consider, which is going so far as maybe publishing a very patient-friendly excerpt of our integrated review, maybe an abstract that could be made available

easily to patients.

The final panel, for someone who's been helping with the modernization and working with this workstream for a number of years now, it's really watering and heartwarming to hear, which is that the FDA internal stakeholders really think that there are a lot of benefits from the integrated assessment. It definitely sounds like it's worth keeping around, and they look forward to the continued implementation.

Some of those benefits mentioned include the benefit of increased leadership engagement throughout the review process, particularly in the early stages, which can really help a team identify what those issues are in those scoping meetings and help to work through them in the joint assessment meetings.

We also heard about the benefits of increased collaboration in the process and in the documentation and that this has been very positive for the teams. However, on the other hand, we heard that this increase in collaboration does take

more time and effort, and that there's a bit of a learning curve, especially with collaborative writing.

I think anyone who's ever been on a team would probably say, yes, it's certainly probably more efficient to work by yourself, and then you get on a team, it takes a little bit longer because you have to hear from everyone and incorporate all those perspectives alongside yours before you can move forward. But in the end, we hope that this is resulting in a much more integrative and beneficial decision-making process for all of us.

I also heard that there was a lot of support for the new review team roles, so the clinical data scientists and the medical editors, and that these have been incredibly beneficial to the review team. It's come to the point, as you heard from Dr. Struble, Kim Struble, if they're not doing an integrated review and they don't have these resources, they really feel the hurt, and they would love to have those for all of their applications.

I also heard there was less overall writing but more intentional writing. This is coming from some of the redundancy that was in the previous documentation that was being done by each individual discipline, writing about the same studies or the same drug development program, which is now there collectively for everyone to refer to. This additional time allows for that critical thinking to come out, which is where that more intentional writing comes from.

Lastly, I heard about the implementation process, which was that it was much more hands-on than they're used to and that they appreciated the patience that the workstream has taken to take a phased approach. I think the benefit is also that for our external stakeholders, we can really take the time to consider all of your feedback and adjust the process, and the templates, and all of the resources and tools that we have as well as we go forward.

A couple of the final parting thoughts, acknowledge those good examples and build those in

the training and resources. External stakeholders, you can help us, too. There are other reviews out there and there are good examples. Let us know about those in dockets or in any other way you can, and we can consider that and build them into our repositories. There's a general excitement to look forward to the expansion of the integrated assessment across the rest of all new drugs and to other application types.

So what's next? First of all, for everyone who's worried or wondering, there will be a recording of this workshop, and they'll make this available shortly after today. I'm not going to promise the exact time, but this shouldn't take too long. However, if you want the transcript, that will take a little bit longer. It will roughly be 60 or 90 days.

There were still some unanswered questions that we couldn't get to in the panels, and we'll try to respond to all of those, and that will be included in the meeting summary. That meeting summary will also include responses to all of the

comments that we receive to the docket, including those that come in after today. So that docket is open until the end of the year, and we do encourage you to go ahead and submit any of your comments to that docket, including if you've already submitted and you want to change something or add additional feedback, please feel free to do so.

We really care about a much more continuous learning cycle with how we're doing implementations across the New Drug Regulatory Program Modernization. An integrated assessment is really no different. What will happen in the coming weeks, and months, and probably even years, is we will take all the feedback that we've received today and that we continue to receive to the docket. We'll of course publish the meeting summary, and there will most likely be some additional comments from our internal/external stakeholders in the realm of that, and we'll use that to inform our continued implementation and also evaluations.

You've heard about the evaluations that

we've done internally. We'll continue to do those. I'm not sure about this, but we may also, depending on the interest, plan a future public workshop to continue to hear from our stakeholders and hopefully continue this cycle or process of continuous improvement so that all of our stakeholders' needs can be met.

Adjournment

DR. BUGIN: So with that, I just, again, want to thank you all and maybe say Happy Halloween. Be safe. There are a couple of links down here. You can go to the FDA for those links on food safety tips and also check out the CDC guidelines for Halloween in the context of this COVID-19 pandemic. So thank you all and take care. Have a nice weekend.

(Whereupon, at 2:55 p.m., the workshop was adjourned.)