Steven Grossman: Thank you and good afternoon. And I appreciate everybody joining us for this webinar. I'm Steve Grossman. I'm the executive director of the Alliance for a Stronger FDA. Many of you know who we are, but for those who don't, we're a group of FDA stakeholders. We represent patients, consumers, health professional societies, trade groups, and industry. In other words, the whole range of stakeholders. But we also represent every segment of FDA, so it's not just food and drugs, it's vaccines, it's diagnostics, it's cosmetics, it's OTC, veterinary drugs.

It's every portion of it so that when we speak, primarily to Congress but also to the public and to the media, we can say that we do really represent the entire stakeholder community and that we are united in our belief that the FDA needs more resources because the world is only getting more complex. And FDA is doing a great job, but it needs the resources to keep up.

So, this is I think the seventh in a series this year of webinars. We are pleased to have Dr. Kluetz, who is going to be here to talk about the Oncology Center of Excellence, which is a relatively new concept. It's not even five years old. They've come a long way, and I think I probably am like with many of you who have fairly good knowledge of FDA but don't know very much about OCE. And so, we hope that this is a great opportunity to learn more.

Dr. Kluetz is a medical oncologist and Deputy Director of the Oncology Center of Excellence (OCE) at the U.S. FDA. In addition to assisting in the strategic and operational oversight of the OCE, he has a broad interest in trial design and endpoint selection to expedite drug development and define clinical benefit in oncology trials. Some of his initiatives include creation of the OCE's patient-focused drug development program and expansion and direction of OCE's efforts to advance real-world evidence, decentralized trial designs and digital health technology. He is also active in regulatory review of Oncology products and oversees important oncology drug labeling initiatives. Dr. Kluetz remains clinically active, caring for patients and supervising medical residents at the Georgetown University Hospital.

The format we use today is he's going to be interviewing himself from a set of questions we've given him, and then we will have as moderators Esther Krofah and Jeff Allen. Esther is from FasterCures and Jeff Allen is from Friends of Cancer Research, and perhaps for relevance, they're both directors of the Alliance for Stronger FDA and we're very proud that they can be with us today as well.

On that note, there will be an opportunity to ask questions. There is a chat function and a Q&A function. Please use the Q&A function if possible. Our moderators will get to their own questions as well as audience ones when Dr. Kluetz is done with his initial remarks. On that note, Dr. Kluetz.

Dr. Paul Kluetz: Great. Thank you very much, Steven. My name is Paul Kluetz and I am a medical oncologist serving as Deputy Director in the Oncology Center of Excellence at the FDA. I'm really pleased to have this opportunity to speak with you, and give you a little bit of an update and background about the Oncology Center, which is the newest center in the FDA. As Steven mentioned, we are coming up on our five-year anniversary.

So, getting started with some of the questions that were posed to me during this introductory talk. How and why was the OCE initiated and how is it evolving? OCE was created following the passage of the 21st Century Cures Act in late 2016. Part of that Act was to authorize the establishment of an inter-center institute for a major disease area and cancer was chosen as that disease area. The Oncology Center of Excellence was born in January of 2017. Our mission is to achieve patient-centered regulatory decision making through innovation and collaboration, and our vision is to create a unified and collaborative scientific environment to advance the development and regulation of oncology products for patients with cancer. And I think that's the key. It's about oncology products, it's not about oncology drugs or oncology biologics or oncology devices. It encompasses all of those products that are reviewed across those centers.

The FDA doesn’t develop or manufacture products, but what we do is we regulate products. And what we can do to assist that is to create a consistent and a nimble and an efficient regulatory environment that can facilitate cancer product development. What that requires is subspecialty clinical expertise, specifically in cancer because it's become a pretty complicated disease.

And that consistent, deep, disease-specific clinical research expertise is what will enable high-quality, rapid, up-to-date trial design advice, and that is the advice that product developers need, whether they're developing a biologic for cancer or whether developing a drug for cancer. And so, to that point, it's all about staff. It's all about the clinical reviewers. And so, we'll talk about that.

Why was oncology selected for the first inter-center institute? I think everyone realizes that one of the most exciting areas in therapeutic development for products is cancer, and that is because we have had decades of sustained basic science research into the etiology of cancer. We understand deeply the biology, the immunology, and the genetic underpinnings of cancer, and that's allowed for very thoughtful product development and a lot of success.

CDER has seen an explosion of approvals across mechanisms: chemotherapy, small molecule targeted agents, and therapeutic antibodies. CDRH has had an explosion of diagnostic tests to select those populations that are most likely to respond. And CBER has had an explosion of immunotherapy biologics, CAR-T cells, adoptive T-cell therapy, regulated in CBER. And while they're all different products, one thing that remains the same is that they're intended for patients with cancer and that's why OCE was created, to create consistency in the development of those products and how we regulate them.

So, how have we evolved? We started with 13 people. I was one of the first 13, largely brought over from CDER's Office of Oncologic Diseases. This includes Dr. Pazdur and the senior executive team in the OCE. You'll hear a common thread that the OCE and the oncology office in CDER are deeply integrated together because the oncology office in CDER has the most extensive oncologic expertise within the agency; we helped develop that expertise and we maintain dual appointments.

The OCE executive group – myself, Dr. Pazdur, my co-deputy director, Mark Theoret, our chief of solid tumor oncology, Julia Beaver, as well as our director of regulatory affairs and policy, Tamy Kim – we are all within the OCE executive group, but we hold dual positions leading the oncology office in CDER. And therefore, we have signatory authority over CDER oncology products and we oversee and supervise their divisions.

So, the evolution of the Oncology Center of Excellence is going to continue to strengthen the OCE's direct review capacity, which currently houses not just the leadership of OOD, but also multiple cross-cutting programs that are cancer specific review consult teams as I'll describe.

I mentioned from the very beginning that it's all about people, and so hiring and recruitment are absolutely critical. There is a significant need for additional sub-specialized cancer clinical

review staff and regulatory project management within the oncology effort. This deep clinical expertise is the cornerstone for success.

And one of the reasons why I think we have been successful in oncology at the FDA is because we set up the oncology office within CDER long ago in 2011 as an academic model. You wouldn't go to Memorial Sloan Kettering or another major academic center and see a general oncologist anymore. It is too complicated. You need to develop specialized teams, and that's how we've structured OOD in CDER.

For instance, there's a specific team that reviews breast cancer. They need to know the breast cancer biology, the subtypes, the natural history… they need to understand breast cancer trial design and specific endpoints, and you need to know available therapies so that FDA reviewers can give the best advice to a product developer, whether they're developing a biologic or they're developing a drug. And so, the field of oncology has changed. It has become more complicated and that reflects the kind of staff that we need to hire.

And so, what does the Oncology Center of Excellence do to ensure that we can hire and maintain and retain that staff? As Dr. Pazdur says, what we want to do is we want to offer careers, not jobs. A career is something that is going to give you longitudinal purpose. What we look to do is to develop our cancer clinical and basic science staff to give them an opportunity to have a long FDA career that's stimulating and that offers them an ability to really provide scientific innovation.

One of the key programs in the OCE that facilitates this goal is the oncology program. The oncology program houses a number of staff that assist us in funding and operationalizing engagement efforts, whether they be symposia or workshops, including IT expertise. This puts our reviewers out in front of the academic field and allows them to be leaders and contribute to innovation and science in their respective fields.

We also have a robust research program led by Julie Schneider in the OCE that funds and supports internal and external research. We funded several million dollars of research efforts last year through the CERSI mechanism at FDA as well as through BAA funding. That allows our reviewers and our staff to develop their research careers. Again, not just following the science, but helping to create the science and collaborate with leaders in their respective fields.

So, it is a part of our mission to develop and maintain this clinical expertise in OCE that will benefit CDRH, CBER, and CDER as those scientists help to review products.

But OCE is more than just career development opportunities. We do provide, and are continuing to build direct review capacity. I'll talk about five programs just to give you an idea of some of the cross-cutting review efforts.

One cross-cutting program is one that Steven mentioned in his introductory remarks: the Oncology Patient-Focused Drug Development Program. What this program seeks to do is to create a consistent approach to how we use patient-reported outcomes or wearable devices in cancer trials to develop rigorous and quantifiable symptom and functional measures for cancer product development.

We drafted a guidance this year for industry that is a roadmap on how to do this effectively. My colleague, Vishal Bhatnagar, who is the associate director leading the program now, has developed a consult service that directly provides review consultation, pre-market consultation, to inform cancer clinical trial design. Over 100 consults have been completed this year, which is a 60 percent increase over last year, so it's exponentially growing. And it's really moved the consults from the more general DCOA staff to the OCE oncology-specific COA consultation group because they are providing a very consistent, very oncology focused approach to how to do this well.

21st Century Cures has also asked FDA to communicate patient experience data from trials. The OCE's patient-focused drug development program has done a great job at doing so. We've increased the amount of patient-reported outcomes, symptom, and function data in our oncology labels, in our review manuscripts, and I think most excitingly, we just deployed a public facing FDA website that provides color visualizations of patient-reported symptomatic toxicities from cancer trials, the first trial being a lung cancer trial for an approved drug.

A second program that is similar in its reach and its excitement right now is the OCE's Real World Evidence Program. There is a real-world evidence effort at FDA led by the Office of Medical Policy, which is creating a broad framework for responding to real-world evidence and its use. What the oncology-specific Real World

Evidence Program is doing in OCE is taking that framework and applying real oncology-specific use cases to fit into that so that we can provide real, actionable advice on how we can use real-world evidence to effectively complement our evidence to support cancer product development.

I was lucky enough to recruit Donna Rivera, a pharmacoepidemiologist from the National Cancer Institute, to run this program and she's done a great job. One important contribution in the short term will be to help to develop real-world evidence endpoints for oncology. One of the most crucial needs right now is real-world response rate. We are collaborating with Friends of Cancer Research and others to do so. The second important thing is to look at oncology use cases and develop a way to think about data quality with respect to the question being asked. We're working with Reagan-Udall on that project.

A third program that is very active is the Pediatric Oncology Program in OCE. That's run by Greg Reaman, who is a world-renowned pediatric oncologist, and he is leading quite a few review processes for pediatric oncology. He is leading our response to the amended Pediatric Research Equity Act, or PREA, and he has provided FDA leadership on the development of the Relevant Molecular Targets List, which is intending to move precision oncology treatments into pediatric trials, and he's really been very successful in that effort. He does many other things as well, but that's just a flavor for the pediatric oncology program.

One of the ways that we use the clinical expertise within CDER and the OOD is to create teams that can go out and help to drive the review and make the reviews consistent across centers. Dr. Theoret, the other deputy director within the OCE, has been really working on the Medical Oncology Review and Evaluation teams, called “MORE” teams.

These teams are initiated when there's a high-value application in CBER or CDRH where they need disease-specific expertise in helping to design a trial, evaluate endpoints or evaluate results from a submission. These teams are formulated, again, with that deep sub-specialty clinical expertise within our OOD disease specific teams and they're deployed to assist in that review and that evaluation.

Finally, I'll talk about Project Facilitate. This is actually taking the single patient INDs and compassionate use work from the divisions and moving it into OCE and its program to basically facilitate

healthcare providers or regulatory professionals in navigating the ability to get an investigational treatment for patients who have run out of options, so-called compassionate use or single patient INDs. Tamy Kim, again, from our regulatory policy and affairs group has really led the charge on that.

I'm sure we'll talk about more of the programs in our Q&A, but I was asked to talk briefly about how the OCE is funded. The Oncology Center of Excellence is primarily funded with budget authority funds that are appropriated on an annual basis. We also have a small portion of funding that is coming from Prescription Drug User Fee Act, or PDUFA, funding. And then additional year-to-year funding may come in through rare cancer funding or through some additional 21st Century Cures money, but that isn't necessarily stable.

So, importantly, to achieve, the next version of OCE or Version 2.0, which in my mind would need to bring in more of that sub-specialty review staff into the OCE and the project management staff, we would need additional annual appropriations or funding that we could rely on on a year-to-year basis.

I want to talk a bit about our funding priorities moving forward for next year with what we have now. Our priorities are consistent with previous years, but we have an increased focus on bringing staff in that can assist with regulatory review. And that's really in response to just an incredible amount of work that's being done in CDER right now and that we need to support if we're going to continue to deploy innovative regulatory programs as well as meet and exceed PDUFA expedited review clocks.

We're really moving towards increasing staff but, of course, that's going to come at the expense of something, and that something will be our operational budget. So, things like the research, the engagement, our IT innovations, and some of our other programs will need to be pulled back a little bit if we're going to do that with no additional funding.

I think we're also going to need, as far as this additional reviewer support, to continue to support and build those cross-cutting programs that I mentioned. Again, the consults that are oncology specific have been really, I think, effective for those that are reviewing oncology products across the centers. And so, there's going to be an increased need for that.

I was asked a little bit about how OCE's work was affected by the pandemic, and I think that's actually an interesting story. No. 1, like every large organization, our most immediate impact was that we moved all of our operations into our homes, and so work at home has become a reality for most, I think, big organizations, and OCE and the FDA is no exception.

I think there's pluses and minuses from working at home. As a supervisor and as someone who's following metrics for productivity, I actually think we're more productive in many ways working at home. But I think as an innovation group and as a group that builds and plays off of each other's creativity, that face-to-face contact, is something that we're looking forward to coming back to, to some degree.

I will say, thankfully, we have an incredible IT support staff, led by Richard Krzysztofik, who has really helped us to continue to engage externally, which is so important for us, using digital technologies.

I think I would say one thing I'm really proud about is Dr. Pazdur's commitment to create an immediate communication plan to patients with cancer and to the drug development community, that despite COVID, the OCE, the OOD, and the oncology effort at FDA is not going to slow down. We are going to get out ahead of this and we're going to continue to ensure that patients with cancer have product development that can help them, and we did have a large communication strategy to that effect.

Finally, I would say that part of COVID that was perhaps a silver lining was catalyzing two important areas of evidence generation. One is real-world evidence, and Donna Rivera, who I've mentioned earlier, and Harpreet Singh, were very interested in spearheading an evaluation of real-world evidence to rapidly characterize how COVID-19 was affecting patients with cancer. That was a project called Project Post COVIDity, and it's resulted in several publications and some of that work is ongoing.

A second area that I find very interesting related to COVID is how prospective clinical trials have been affected, and what do we do to continue those trials and what do we do to get trials started in such a rapid way? There were a lot of increased efficiencies that I have seen. Clearly, hybrid decentralized clinical trial designs were deployed successfully using remote assessments with digital health technology. I'm very interested in exploring that success and continuing to support, where appropriate, use of decentralized

clinical trials or hybrid trials moving forward.

So, I will conclude by saying that, in summary, OCE was created to provide consistent sub-specialized clinical oncology advice and review across the product centers. I think we've been successful at growing our programs and our footprint and our value at FDA. I would reiterate that the success, I think, of any organization but particularly of the OCE is its staff. We are reliant on recruiting and developing and retaining high-quality, hard to find clinical and scientific cancer researchers so that we can develop careers with them. So, if people want a career in cancer research, they should come see me in the OCE.

I do think, unfortunately, there's a tension between innovation and expedited programs and just the volume of work and getting the work done. We can talk about some of this in the Q&A, but expediting reviews ahead of PDUFA goal dates, using regulatory programs like real-time oncology review or breakthrough therapy designation or Project Orbis do require additional meetings and that requires additional boots on the ground. So, to continue the timelines that oncology is used to seeing, especially as the environment for development becomes more complex with available therapies, I think we're going to continue to need to staff up and have resources to do so.

Our OCE near-term priority, in that regard, is to staff up our review groups within OCE to help the centers. And so, we are moving more towards personnel rather than operational budget, at least while our budget remains flat.

I'll end just by saying our overarching priority, as Dr. Pazdur has said, is to put patients at the center. They're at the center of our mission statement. They're at the center of our vision statement. And I just want to end with a huge thanks to many dedicated scientists at FDA, not just in OCE, not just in OOD, but across the centers – statistics, clinical pharmacology – the FDA is an amazing place to work, and I'm happy to be able to collaborate with those scientists.

So, thank you, and I'm happy to answer some questions.

Jeff Allen: Great. Thanks so much for that overview. It was a very helpful way for us to kind of reorient to the activities of the OCE. A couple of questions to launch into our next segment here. I'm familiar with some of the projects that OCE has undertaken over the last couple of years, and you've just scratched the surface of those, so I hope

we'll be able to dive into a few more.

But you mentioned early on, when you first joined FDA, it was perhaps maybe under 20 or so medical oncologists that you were joined with and that's exponentially grown. Can you just talk a little bit about how different the oncology function is at FDA now in terms of engaging with external stakeholders? You've summarized some of the research that's underway, but I think it is a growing function of how you engage not just with the sponsors but with the external research community.

Dr. Paul Kluetz: Sure. Thank you, Jeff, for that question. I think probably what we're known most for is how much we get out and engage. And that isn't necessarily so new, but I do think it's grown over time, and I actually think that the Oncology Center of Excellence was critical to really give us the oncology communications group that we have, our IT group that we have, and as I mentioned, the oncology program in order to really help us facilitate being able to do mini symposia, workshops, et cetera.

So, a couple of the ways that we engage that I think are new and they've evolved over time, as I mentioned, is getting people out in front of groups that are not just internal FDA groups. We wanted to get out of a black box and get into more of a transparency mode and a collaborative mode. And so, I think you'll see at most major scientific meetings in oncology, whether that be the AACR or ASCO or ASH, there will be regulatory tracks with FDA oncology presenting new reviews or looking at various endpoints or looking at challenging development spaces.

We have an incredible outreach to patient advocacy and nonprofit groups, and we've done a lot of not just qualitative exercises but important scientific work. That includes project with Friends of Cancer Research, that includes efforts with Lungevity and other advocacy groups. There are a couple specific programs that are targeted to engage some of the more challenging and underrepresented groups.

You may have heard of Project Community, which is a project led by Rea Blakey. She has been working to really reach out and understand the challenges and the opportunities for patients with cancer in underserved communities. Project Silver is a group that is led by Harpreet Singh looking at how we can engage the older cancer population scientifically and making sure that those subgroups are in clinical trials. Lola Fashoyin-Aje is working

collaboratively with Rea and Project Community on a program called Project Equity, which is taking what we learn from that engagement and making it into actionable trial design and policy advice.

So, there's so many ways that we're engaging that I think are far more than there were when I started. And that also includes inter-governmental efforts. I didn't mention the National Cancer Institute or NIH, but we work a lot with them – we have regular meetings with CTEP and we have some really exciting scientific collaborations with the NCI clinical center.

Esther Krofah: Well, thank you so much for that. Certainly, quite helpful to better understand how you're engaging. Could we talk a little bit more, Dr. Kluetz, in terms of when the product applications come to OCE and at what stage do they come to OCE. Are we talking about IND? Are you involved throughout the entire product review cycle? Do they go directly to the centers first and then to OCE? Why don't you just walk us through what that process looks like?

Dr. Paul Kluetz: Sure. So, for Version 1.0 of the OCE, we are sitting on top or alongside the other three project centers. The applications will come into the center that they are primarily being reviewed by. So, if it's a CDRH product, it goes to CDRH. CBER, biologic goes to CBER. CDER obviously goes to the CDER regulatory project managers.

Now, in CDER, again, because we're so intimately engrained in the oncology office as part of our role as acting supervisors there, we see everything that comes into the CDER group from the very earliest IND, and we're actually overseeing those divisions. At CBER, we generally have started to think about the most high-impact products. So, if there are expedited programs in the pre-market space, if they're looking at SPAs or large clinical trials that are intended for regulatory submission, we'll weigh in on those trial designs with them. And then, obviously, if CBER gets an oncology submission, we'll deploy a MORE team to assist in the review.

So, the way that the actual logistics works is still very similar to how it had in the past. It goes directly to the product center and then OCE will deploy that sort of sub-specialty team as necessary. And mostly, it's CBER that's going to get the MORE sub-specialty oncology team from OCE and CDER.

Esther Krofah: If I could just ask a follow-up question to that, and then I'll give it back to you, Jeff. Is there a trigger that happens when an application

has been submitted to any of the appropriate review divisions and centers?

Dr. Paul Kluetz: So, to my knowledge, there's no actual trigger as far as an IT solution that flags a submission or anything like that. What this really shows is it's critical that we have good relationships across the centers. In general, like I said with our sort of cross-cutting consult reviews, they're becoming so useful that they're being sought out. And that's what we want. We want people to feel that they're getting high-quality, efficient advice that's helping the development of their products across the centers and that's sort of created a quality control for us in some ways. We really need to provide value, and I feel like we're doing a good job doing so.

Jeff Allen: You mentioned that one of the funding priorities is investment in growth of additional experts. In thinking about that workload, the oncology group has obviously been involved in the implementation of the breakthrough therapy designation amongst other expedited programs. At least for the breakthrough designation, about half of all of the approved drugs through the program were in oncology, so while it's not, certainly, isolated to oncology, it is perhaps a little – maybe a little heavier applied in that case, probably largely because of the science.

But in terms of the intensity of that workload, does implementing the breakthrough implementation, is that more resource and time-intensive or is it just compressed as you've seen it sort of evolve with your staff?

Dr. Paul Kluetz: You know, I think it's both. I mean, I think when you compress the timeframe, you're getting more meetings in a shorter period of time. And I also think that there's actually more meetings. Part of the benefit of breakthrough therapy designation is more frequent consultation with FDA and allowing us to really help facilitate that product along the way.

So, I do think, first of all, your point about the fact that many breakthroughs are in oncology is absolutely accurate. It's not just breakthrough therapy designations. It's actually just the entire workload in CDER, it is 30 to 40 percent oncology. So, there is a huge workload challenge. And deploying the expedited programs on top of that – just off of that workload, in general, is causing some strain and there's no doubt about it.

We just had a meeting today where I talked to the reviewers in the

office to say we will continue to develop efficiencies, identify ways to get more staff, and really, we have to prioritize how we deploy expedited programs until we get staffed up because it's really hitting a critical mass.

Jeff Allen: So, fair to say that for all of these different programs that live alongside of the review functions, having the resources to support that is essential for their continued success.

Dr. Paul Kluetz: Yes, particularly if we're going to deploy them at the frequency that we do now, or at the threshold that we do now. I know for a fact that if we have a transformative therapy that is going to completely change the standard of care in a disease area, we don't need an expedited program in oncology at FDA to use an all hands on deck approach. We want that product to come out should there be substantial evidence that the effect is large and the safety is acceptable.

Really, the question is where is that threshold going to be for deploying things like real-time oncology review, Project Orbis, and approvals months before the PDUFA goal date.

Esther Krofah: Dr. Kluetz, we're going to take some questions that are coming in through the Q&A, and certainly, a few have come in. one that I wanted to start with, and it's a bit of a combination question here. You talked about your centers and focus on 1.0. Can you talk a little bit about the move to 2.0? You talked about, at the beginning, you were about 13 staff. You've obviously grown a bit, but what is the resource capacity like? When you talk about 2.0, how do you think about that differently from a resource perspective?

Dr. Paul Kluetz: As I mentioned before, we can do various things moving around the current funding that we have between FTEs and operational spending, and at least acutely, that's what we're likely going to do. We're going to move more towards more boots on the ground and probably have to pull out some of the operational budget and research and other things.

The second version of OCE is going to require a much larger discussion in the agency at higher levels to really determine what the right organizational structure is. And that includes to what extent will the review of cancer products move more into the OCE rather than it being more directly the review.

There's no formal plan currently for OCE 2.0. Obviously, we've had

some changes in leadership or we're going through changes in leadership at the FDA, so we need things to settle down and then really have a frank discussion about what folks want to see for OCE 2.0.

Jeff Allen: One additional project that you mentioned briefly, and there's a couple of questions on it. Can you describe a little bit more around Project Optimus, which I think is a real transformative and innovative project that you guys have been leading? And specifically, if there are plans for guidance documents into the future that will help inform that?

Dr. Paul Kluetz: Sure. Project Optimus, another sort of Latin- termed project, is really looking to optimize dosage in cancer therapeutics. I think it's well known that when you look at tyrosine kinase inhibitor oral therapy in oncology that there's a high percentage of patients that need to have their dose modified. And that doses that go into late phase trials are often on the high side, perhaps too high. And so, more effort could be applied and should be applied to identifying a more tolerable dose.

I think, as far as where we're headed with that, currently, we're doing a lot of ground work to identify what we think would be optimal and feasible for both pre-market and post-market dose optimization. That includes looking at trial design and statistical principles for maintaining efficacy while identifying tolerability and safety. And I think all of that early work will then be applied when we feel comfortable with more formal guidance to industry, but that's a step that we take after we do our groundwork.

Esther Krofah: Paul, you talked about earlier real-world data, real-world evidence. What are the learnings from COVID-19, and certainly some projects that were initiated and continued partnerships that you have with regard to that? Some questions are emerging about just your take on the data quality. What are you seeing of the data quality that's coming in through RWD/RWE? Where are there opportunities, potentially, to expand upon what the range of data could be that come in through those mechanisms?

Dr. Paul Kluetz: I think the effort that Donna Rivera is undertaking and I'm supporting with Reagan-Udall is actually going to address this directly. And when you talk about data quality or sometimes what we call the fitness for purpose – is the data fit to be able to support a research objective? – it has a lot to do with the question that you're asking.

And so, there's opportunities right now for real-world evidence, and we have used real-world evidence, for safety and pharmacovigilance, for characterizing the natural history of the disease, for understanding use data. For instance, how often a drug was used, etcetera. I think the challenge becomes when you want to use RWE to provide substantial evidence of efficacy to support a new indication for a cancer product. And that's where everyone would like to go, but before we do that, we need to understand what are the data elements that are necessary in real-world evidence to provide us with a secure understanding of whether it's fit for purpose.

And it's more complicated than just the objective. Even if the objective is efficacy, what is the endpoint? Is it real-world response rate? Is it time to next treatment? Is it overall survival? And as Jeff and Friends of Cancer Research know very well from all their work, there are very different challenges in what sorts of data you need from EHR to support the different kinds of endpoints.

So, I think what we're seeing is the beginning of understanding real-world evidence and how it can be used to support and complement our clinical trial data. I think we're going to learn a lot in this next year or two with Reagan-Udall and we developed this program specifically so that we can concentrate on oncology, concentrate on the oncology endpoints, and try to move the field forward.

Esther Krofah: Just to follow up on that quickly, when we think about the impact of oncology and health equity, obviously we see that disproportionate impact in certain communities. Do you think that RWE offers the opportunity to close the gap in evidence generation in communities that are historically underserved?

Dr. Paul Kluetz: I think, as I mentioned earlier about the silver lining of COVID, I think that there's a couple of things that are happening right now that could do just that, help us understand better subpopulations that are typically underrepresented in our standard prospective clinical trials. One of them is real-world evidence. But again, we still want to make sure we understand the endpoint and make sure that the efficacy signal we're seeing from the real world can be relied on.

But another opportunity is decentralized clinical trials – so, maybe we can get trial conduct out more to where patients live and reduce some of those barriers that may be contributing to who are being underrepresented in prospective clinical trials as well. I'm hoping

that we're going to be able to attack that challenge from multiple angles, not just real-world evidence. But I agree with you that that this area is a potential use for real-world evidence.

Jeff Allen: I'm going to try to wrap together two sort of nuts-and-bolts operational questions here. If you could sort of provide a little bit more detail, you mentioned this, but it's really around how OCE functions with the different offices and centers. So, the first around things like orphan products and pediatric reviews and how PREA requirements – is that something that is handled through the Office of Orphan Products or is that something that Greg and the OCE team get into?

And then along those same lines, in terms of BLAs and PMAs that are at CBER and CDRH, respectively, are there components of those applications that OCE is responsible for approving or is it more of just a consult?

Dr. Paul Kluetz: With respect to the real in the weeds pediatric oncology review and the sorts of things that Dr. Reaman is helping, he's more facilitating rather than directly reviewing in some cases. And in some cases, he's really very involved. For instance, the subcommittee for PeRC. And he's driving a lot of of the policy for pediatric oncology.

With respect to CBER and how we assist in the review of the CBER products, again, we create the MORE teams, and we do have the clinical sign-off for oncology BLA applications. And most of the time – we haven't had a situation where we've disagreed, and it's needed to go to sort of an arbitration. But for the most part, currently, we do not have in CBER the full product sign-off.

Esther Krofah: And you talked about decentralized trials, and you've talked about even one of the silver linings from COVID, the pluses and negatives of the working from home. Are you expecting to hire more staff across OCE in this hybrid decentralized way? Does that give you more flexibility with retaining talent? For example, if you have a team across the U.S.

Dr. Paul Kluetz: The agency in its entirety is actually trying to wrap their hands around this – what I find as an opportunity. But it's also a completely different way of thinking for FDA. Have there been FDA employees that were allowed to work from a remote location? Florida, for instance. Yes. But it's been much more rare, and it's usually needed to have some sort of reason.

I think that this experience has really shown that people can be just as effective, and perhaps even more effective in some cases and productive, working from home. So, I think that is an area of evolution of thought in the FDA at large. My guess is that there will be more flexibility to allow that sort of approach to have more flexible workplace setups.

Esther Krofah: And just if I can follow up there. Earlier, you talked about you had 60 percent more consults, right? With the Patient-Focused Drug Development meetings. How have you managed that virtually? Have you found that that's more efficient? People don't have to travel to come to White Oaks. I mean, what –

Dr. Paul Kluetz: I think it's incredible how you can manage to communicate on Zoom and do so very effectively. I remember in the beginning, it was a little herkie jerkie and people didn't know how to break in. And I really feel like – and I'm sure you've all experienced the same, that our ability to communicate virtually has just become so much better.

So, I find that the consults are working very well. I mean, some of them – ideally, if we have a written consult and people are fine with it, we may even not need a meeting. But where we do and where there's questions, I find that the communication has been very good, and we've been able to facilitate that sort of face-to-face interaction virtually, like we're doing now.

Jeff Allen: Building on some of the things that you mentioned around being out at scientific meetings and involved in the research process and with people on the ground doing research, I'm curious, is it unique – do you see that as a unique function of the OCE to have those opportunities? And also, with the idea of sort of keeping your staff really up to date with a very rapidly evolving field like oncology – we mentioned in the intro that you still are a practicing oncologist, as are many of your colleagues. Is that unique in terms of compared to other therapeutic areas as well at FDA?

Dr. Paul Kluetz: Well, it's hard – it is a little hard to stay clinically active as an oncologist. Some people do have oncology clinics, sort of a second opinion clinic, where there's not as much follow-up. Oncology is so unique. One of the reasons I went into oncology is because the relationship that you build with patients and their families is so tight and so intense, and you have to be there for them. So, I don't practice oncology when I go to Georgetown for that reason. I don't feel like I could do it to the way that I would want to do it. So, I am a hospitalist. I work with in-patient folks that are sick across cancer

and other problems.

Is continuing to practice medicine unique to FDA oncology reviewers? No, because I know that one of my colleagues in infectious diseases at FDA works with me at Georgetown. I think people that work at FDA that are clinicians like to get back to patients and remember why they're doing this. Why is it important to have a better therapy for some of these diseases that you see people getting admitted into the hospital for? It reminds you of the mission – it puts the mission up front.

As far as the science, I personally find that one of the most rewarding parts of our job, the science and the engagement. I do believe that's why we retain people in oncology– we don't just say it's okay for you to do it [research and engagement], we actually create ways to allow you to do it and we want you to do it. And rather than keeping up with the science, we're trying to be *involved with the science* so that we're right there helping to create it. And so, I think that that's been successful. That's been something Dr. Pazdur, as a former fellowship director at MD Anderson, feels very strongly about. Career development, science, making this a career and not a job.

Esther Krofah: And to follow up with that, how has the field of oncology evolved from your perspective over the last five years? Certainly, we've seen significant changes in the therapeutic options that are available, and obviously, you've talked about going to these meetings and these conferences and being right there. Rather than keeping up with the science, being involved with the science itself. How is that reflected in the staff as you see the change and evolving over the entire landscape?

Dr. Paul Kluetz: Boy, the difference between now and 2010 when I started is amazing. First of all, I think it's become much more challenging to develop drugs because there are so many more available therapies. The complexity of what a drug development group needs to do now compared to 10 or 15 years ago, where it was possible to run a true placebo-controlled trial in some cases in multi-refractory cancers.

I think what we're going to see, and I don't think it's a bad thing, is more head-to-head trials. And that is why I think dose optimization and better measurements of symptom and functional data, really exploring the whole picture of the drug and understanding what its value is more than just an incremental PFS or OS advantage is going to become more important. I also think pragmatic – being more

pragmatic with prospective head-to-head trials, doing them in a more efficient way, is also an opportunity.

So, I think the big difference now is available therapies. I think the difference now is great science. I think the difference now is combination therapies. I think it's made it more complicated, but I think it's still an incredibly exciting time.

Jeff Allen: I know that the OCE, in concept, is something that you and colleagues and Dr. Pazdur have thought about for quite some time. But as you mentioned, they were sort of formalized five years ago. It was kind of a little bit of a grand experiment of this type of approach. As you think over those years and toward an Oncology Center of Excellence 2.0, are there things that you would have done differently or particular challenges that were encountered?

Dr. Paul Kluetz: I don't think there's anything I can think of that we would have done particularly differently. I do think that the spirit of this was to have the review function within the oncology center and to deploy the reviewers into different product centers and have the product-specific expertise and the manufacturing expertise in the product centers be complemented by this deep bench of oncologists within the oncology center. That was pretty aspirational when it very first started.

What I've come to realize over five years, is that it's an incremental process. You have to show value, you have to develop programs, you have to create relationships across the centers. And I think we are at somewhat of an inflection point on making a decision on where we need to go next. But I'm feeling very confident that the programs we have in place now are adding value and have been successful along the way.

Esther Krofah: I have to say, I have enjoyed learning about the different projects. Right? Project Community and Project Orbis and all of the different initiatives that are going on. And certainly, creative naming structures there. Is there something unexpected that you think folks should know about? What OCE does that may not be well known by the public but yet quite important to how you operate and function and how you achieve the mission?

Dr. Paul Kluetz: There's are two things that I'll mention that are somewhat lesser known. Actually, one of them showed up in the chat. But some of the internal things we do, I think, are representative of who we are culturally.

One of them is something that Dr. Pazdur really wanted to do called Conversations on Cancer. And it brings in people from outside as well as FDA folks who have had a personal experience with a cancer disease, and they talk about their journey and their challenges with that disease and they talk with groups outside who are doing research in that disease and it can cover multiple different topics. It brings up the point that we're on a mission to work on a disease that is affecting everybody, even people that work within FDA, and I think that's a really special program that Rea Blakey runs.

A scientific program that's not well known but that I actually talked about at the Friends of Cancer Research annual meeting as one of our early programs that I find interesting is Project Catalyst, which is a smaller group who is really interested in trying to provide some consultative advice to really small, early companies that are trying to do something really innovative. Typically, these are in the biologic spaces. Really early biotech companies that don't have much experience, and do not understand FDA regulatory pathways and really need the most assistance.

Some of the most exciting and groundbreaking therapies are going to arise in that startup space, and it's hard for that group to get involved in FDA and understand FDA. So, Mark Theoret and Jeff Summers at FDA have started a program to really try to think how we can educate those groups that are really investigator/community type level that really need the help and the guidance. And so, I think that's an interesting program that's not well known.

Jeff Allen: Well, Paul, I want to make sure that we wrap up on time here for folks, but really do want to thank you not only for joining us today and sharing your experiences and helping the Alliance provide additional information about all of the very important and timely things that the OCE is doing, but for your continued leadership at the FDA and with your colleagues to really drive an exciting field forward and the outreach that you do on behalf of FDA toward the patient community and development community is really remarkable.

So, thanks for joining us today, and I think we can probably wrap up there unless there's other announcements that need to be made. But I'm not aware of them.

Esther Krofah: Yeah, just want to add my thanks as well. Really fascinating conversation. Thank you for walking us through all the incredible

work that OCE is doing.

Dr. Paul Kluetz: Thank you, Esther, and thank you very much, Jeff.

Jeff Allen: And thanks, everyone, for joining us today. Keep an eye on your emails for some additional Alliance webinars to come, but have a good rest of the day.

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Duration: 56 minutes