

Ron Bartek: So, good afternoon, everybody. I'm Ron Bartek. I'm President of the Alliance for a Stronger FDA. I'm joined today as usual by Steven Grossman, the Alliance's Executive Director. We'd also like to welcome other Alliance members that are in the webinar plus media and a number of guests who have joined us today.

First, a quick word about the Alliance for a Stronger FDA. We are a multi-stakeholder coalition that advocates for increased appropriated resources for the Food and Drug Administration. We've been an important force in the doubling of available annual budget authority resources from about 1.6 billion dollars to more than 3.2 billion dollars. And we are the only advocacy organization focused on resources for both food safety and medical products as well as the other components of the FDA mission. Our members include consumer and patient groups, research advocates, health professional societies, trade groups, and industry. We have about 150 members and always welcome more to strengthen our advocacy and educational efforts.

In regard to the procedures for today's conversation, our speaker has kindly agreed to the format that's worked so well in our earlier webinars. In other words, he will interview himself based on questions the Alliance has provided him, followed by ample time for him to answer some of your questions. You may submit such questions by clicking the Q&A button at the bottom of your screen.

Before introducing today's speaker, the Alliance would also like to thank Ms. Tonya Diaz and Mr. Justin Weincek of the speaker's staff for their help in coordinating this event.

I now have the distinct privilege and honor of introducing Dr. William Slikker Jr., the Director of the FDA's National Center for Toxicological Research since 2006 in fact. Dr. Slikker received his Ph.D. in pharmacology and toxicology from the University of California at Davis. He holds adjunct professorships in the Department of Pediatrics, as well as the Department of Pharmacology and Toxicology at the University of Arkansas for Medical Sciences. He has held committee chairmanships or elected offices in several impressive scientific societies, including the Teratology Society, where he served as president, and the American Society for Pharmacology and Experimental Therapeutics. Dr. Slikker is also the co-founder and past president of the MidSouth Computational Biology and Bioinformatics Society. He is currently associate editor for NeuroToxicology and

associate editor for the “Environmental Health” section of Experimental Biology and Medicine. He is the past president of The Academy of Toxicological Sciences and the Society of Toxicology. He received the 2014 George H. Scott Memorial Award from The Toxicology Forum and was selected to present the Warkany Lecture at the 2015 annual meeting of the Teratology Society. In 2019, Dr. Slikker was honored by the Academy of Toxicological Sciences with the prestigious Mildred S. Christian Career Achievement Award.

You can certainly see from all this how Dr. Slikker’s background, his training, and achievements along with the strengths of his National Center for Toxicological Research make him an ideal speaker to address some of the most important issues currently facing the FDA and our Alliance. From the perspective of a patient advocate, I would just list one such pressing issue as the toxicology challenges impeding rapid progress in one of our most promising therapeutic approaches: gene therapy. Dr. Slikker, thank you very much indeed for all your service and leadership today. And for agreeing to speak with us today. The floor is all yours, sir.

Dr. William Slikker: Well, thank you so much, Ron. It’s been a real pleasure to get a chance to know you and I also thank you for the kind introduction. I really appreciate that. is an important task, and that is supporting FDA and we really appreciate your efforts in making that happen.

I wanted to spend time providing a little bit of an overview on what NCTR does, what the National Center for Toxicological Research does within FDA. We are one of the enters —actually, one of the older enters. We just celebrated our 50th Anniversary about a month ago, and we’re very proud of that. We had the privilege of having the Commissioner of the FDA provide opening comments along with the Governor of the State of Arkansas and many others including Chief Scientist at FDA, RADM Denise Hinton. So, it was a great ceremony, and we appreciate that support and your support as well.

What the NCTR does for FDA is to provide data for FDA decision-making. We also help validate and explore new technologies, emerging technologies to generate data. But before those can be used to generate data, they have to be useful — found to be useful for FDA decision making. And we do a lot of work in that area of exercising those emerging technologies and making sure they’re appropriate for FDA use.

The other thing is that we work with all the product centers and offices of FDA. So instead of having just one product line like foods or drugs, or veterinary medicines, we work with all those different centers, including the Office of Regulatory Affairs or ORA. And we do this so that we can find out what are the issues that are facing those various product centers and help in solving issues by doing experiments, or doing surveys of literature, or discussing and consulting with them about issues they face.

And this is the fun part of the job — trying to help individuals throughout FDA solve problems that they need to have solved. So, one of the things I wanted to mention right up front is, how do we go about doing that? How do we find out what the other centers and offices need and then approach those problems? And the way we do it is through a two-step proposal-review process that first begins with a concept that is usually no more than two or three pages. And we float that out to the various product centers making sure that those that have interest in that area or that particular proposal, get a chance to review it. But sometimes the proposal idea comes from the other enters. Which is great. In other cases we develop the concept and then see if it's important to FDA. So, the critical step here is that we need to make sure that what we're proposing is going to be important to FDA and answering a critical question. If it does not do that and we don't get from one or more of the other centers then we don't do the project. It goes away. But if they say, "Yeah, that could be interesting. That could be important for us to know. And as a matter of fact, we need to know that tomorrow." Well, then we jump on that and we develop a full proposal which goes back to those same individuals within the other enters or offices and gets reviewed and improved. And often we can find individuals that want to serve on that project. We call them collaborators or co-investigators, and they're going to be with us every step of the way: developing the proposal, fine-tuning, getting the proposal approved, then executing the proposal, and writing up the data coming from the proposal, writing up the findings, publishing those findings, and being a co-author on that work. But, of course, they are share every step of the way with the rest of the FDA so that components can be used right away if it's pertinent to their particular needs. So, that's a way to make sure that we stay lock-step with the needs of FDA and answer research questions that apply to each one of the enters or offices.

So, just to make sure that you understand how critical it is to us

that we have actual reviewers or researchers from the other centers or offices on our proposals, over 60% of our research includes at least one other FDA center or office. We actually have FDA scientists who have enough time and energy to spend working on that proposal with us, and that is really key. It also means that because their supervisor had to sign off on that agreement, that we have support from the upper reaches of FDA for them to be engaged in that work and to move forward with us. So, we really appreciate that support as being critical to making sure that we're on target for the work that we do at NCTR on behalf of all the centers and offices of FDA. So, with that background, I'd like to get down to some basic kinds of questions.

And one may ask why Bill Slikker, Director of the National Center for Toxicological Research, is speaking to you from Jefferson, Arkansas. Actually, we're six miles away from Jefferson in the north of Arkansas. This is pretty much in the central south part of Arkansas. It's a long way from where White Oak is and the other parts of FDA that are in the DC area. And one of the reasons for that is that this is really a prime place to do research.

First of all, it was a facility that was already active back in the 50s, 60s, and very early 70s. In fact, in 1968 the activity that was done here, which was the production facility for biological weapons, was curtailed and set aside by then-President Nixon. And ironically enough, a few years later in 1971, it was re-opened as the National Center for Toxicological Research. The buildings were prime for that. And we're talking about 500 acres —plenty of room — all owned and operated by FDA that can be changed to fit our needs. These buildings are renovated now, but the basic structures were there, over 30 of them on this prime piece of real estate out here in the north located right next door to the Pine Bluff Arsenal. We share about two thirds of our fence line with the Pine Bluff Arsenal — great neighbors to have at any time but certainly when you're doing research on behalf of FDA. So, it's a great location. And it has a history that now spans 50 years as the NCTR, which is pretty remarkable.

The other thing that often comes up is: what are some of the things that have been really important to the development of NCTR? And some of these things really have to do with the ability of getting our work done. That is, we have the ability to do work in [animal](#) models. We have the ability to do research with cells in culture. We do a lot of research with computer-simulated work — artificial

intelligence, as it's now being called. And it really is an exciting area to combine these different forces together

For example, I still recall some 15+ years ago that I got a phone call from then-Director of the Center for Drug and Evaluation and Research, Janet Woodcock. She mentioned that there was some interest in using ketamine, which is a dissociative anesthetic which has great attributes because it has quick onset and short duration. It doesn't cause respiratory depression and is very useful for anesthetic work. But she had a question about whether it could be used safely in children and whether that was a good idea. So, between the researchers there at the Center for Drug Evaluation and Research and our researchers, we came up with a plan to evaluate that important question; is there any liability for exposure to ketamine in children? Together we addressed this issue in a variety of animal models, cells in culture, et cetera, and we came up with a very good answer to this issue and as with many agents often times the answer is related to the duration of exposure and the dose of exposure to a particular agent, in this case ketamine. This was all worked out very nicely in a series of collaborative studies over 15 years. In fact, work is still ongoing — publishing many papers and consulting, of course, with all those at FDA that are interested in this topic. And as it turns out, there was some guidance that came out from this work about the safe use of anesthetics in children.

So, that's just one example of the kinds of things that we do that really allow us to make an impact, a positive difference for the FDA in terms of its decision making. And it turns out, also making an impact on clinical practice and the use of anesthetics in children. Now this is definitely something that's in front of the clinical population. We just had a discussion with several clinicians and other researchers about this yesterday and how it impacts their use of anesthetics in children and what we're doing to try to further improve the situation for future generations.

So, I just want to provide examples of the other many things that we develop here at NCTR. But it's not all in the pharmaceutical area. We do a lot of work with foods. And one example of that is domoic acid. I don't know if you're familiar with domoic acid, but it's an agent that unfortunately accumulates in seafood, especially filter feeders. And several years ago — a generation ago, it caused some major problems in the [memory and](#) learning of an adult population, and it was because they ate a lot of seafood, in this

case, shellfish. This population not only lost their ability to remember what was going on, but unfortunately, one of them passed away. This was linked back to exposure to domoic acid, which is a small molecule produced by phytoplankton in the ocean, and when it's produced then it can accumulate in shellfish. And when people eat the shellfish you can have issues. Later it was also shown that it could be a problem in sea lions and other sea creatures as well. In fact, even some go so far as to say that it was part of the background for that famous thriller by Hitchcock, *The Birds*, which also, as you know, went awry after consumption of something. And one could attribute that perhaps to domoic acid.

So, there was an interest in learning more about this. We did studies closely aligned with the needs of the Center for Food Safety and Applied Nutrition, and came up with some acceptable levels using our animal-model studies and, in doing so, we generated a lot of other data in combination with data from other places. Now, seafood is analyzed for domoic acid and acceptable levels are met so that we do not have those kinds of issues. But that's just another example of how we work with other centers, in this case, with the foods area.

And then of course, we had a venture with many people at the Center for Veterinary Medicine on other agents that can cause pet illness, and we know about this now as melamine and cyanuric acid combination. We studied that with researchers from the Center for Veterinary Medicine (CVM), and not only looked at the adult exposure susceptibility, but also developing animals' susceptibility and provided data to support action that may be needed to be taken by CVM. And again, it resulted in award-winning work that was done between the two centers, NCTR and CVM, to move that area forward and make sure that we had safe pet food for our pets.

Those are some examples that sort of tell you about how we come up with projects, how we get those evaluated very thoroughly by those that need the work done within the other parts of FDA, and then do the work together so it can be useful for their decision making.

Another area that comes up is how we generally organize and fund the research. Well, we're organized from a research perspective around certain areas of expertise, and so, we have a Division of Microbiology which, right now, thinking about the microbiome,

there's a lot of interest in that particular area at this point in time. We have a Division of Neurotoxicology that I was fortunate enough to initiate back in 1993 and it's still going strong. There's a lot of interest there, especially with the developmental neurotoxicology potential of certain agents. There's also a Division of Systems Biology, that really began with my predecessor, Dan Casciano, [putting] this together. And the idea was to really look at the omics revolution. This division included specialists in proteomics, metabolomics, and genomics that could be so useful in moving the field forward when it came to understanding more about omics and how it influences not only drug development, but drug safety, as well as safety of other agents in the environment, including food for livestock.

Another one is the Division of Biochemical Toxicology which really focuses on two things — exposure, that is understanding the levels of exposure to certain agents, and cancer endpoints that may develop because of those exposures.

Another division that I want to mention is the Division of Genetic and Molecular Toxicology. This division has been very active in developing assays to look at genetic susceptibility. And they actually developed assays such as the Pig-a assay that's going through final review now and is being evaluated by OECD as a worldwide approach to looking for genetic abnormalities. It's a really nifty analysis because you can use red blood cells and cells from the blood system for analysis, meaning that you can take samples sequentially. You can take samples from human as well as animal models and then compare and contrast those data to understand the susceptibility to a particular agent. So, this is a really fantastic new assay. But they've developed many of these methodologies for genomic analysis over the years.

And the final division I want to mention, our sixth one, is the Division of Bioinformatics and Biostatistics. I felt over seven or eight years ago that we needed to reemphasize this area. It's always been important to NCTR to have a highly dedicated staff on computer science, on the use of various kinds of machines, tools, and that sort of thing. But by creating a division of bioinformatics and biostatistics, we really brought together 30 or 40 really excellent researchers to address this issue. And now artificial intelligence has become such a key term. Obviously, we've been doing that sort of thing for years, but that terminology now has really caught on, and it's a fundamental aspect that

machine learning and bioinformatics are critical to the concept of artificial intelligence. So, that's the sixth division I wanted to mention.

So, we're organized around these divisions but they all work together to solve problems. Often the bioinformatics folks work closely with the people in the neurotoxicology to come up with better ways to assess agents and that sort of thing. So, it's a combination of efforts that really makes it work. And all these divisions of course work with the various parts of FDA, the other FDA centers and offices.

So, that's sort of how we're organized to get our work done. Now how do you fund such an interesting alignment of individuals?

Well, we do it by funding actual research proposals —and those proposals, as I mentioned earlier, go through all those steps. The initial phase is ensuring that the concept is of interest and is important to FDA, and then the full proposal is reviewed and approved. And that's also when we determine the budget so we know how much it's going to cost because we've been doing this for 50 years and we have a good idea how to cost things out. And then we say, "Well, that's the budget it's going to take to get that work done. Here's the timeline. Here's the personnel that we need. Here's all the funding that we need." And then what we do, we try to fund as many of those that are approved. Only those that are approved can be funded and completed. And usually, they are completed in a two-to-three year timeframe, although some of those may require an extra year or so. But the idea there is to make sure they're fresh and they're still currently important to FDA when they're completed.

So, that's the way that we fund our projects. And we'll get into that a little bit more as we go forward. In fact, some of the questions are really built around an idea or current need: what are the NCTR FY 2022 budget priorities?

We talked around this issue, but one of the big issues is biomarker development and validation. Now, what is the utility of a biomarker? Well, it tells you something about the state of an individual or state of an animal and whether they have a health issue or not. And so, it's an indicator of health status and/or a biological level of some entity that's important to health status. We've really worked on these biomarkers along with many other

people around the world, of course. But the idea is to find out which biomarkers are really going to be of importance. Let's say maybe micro-physiological systems, which are getting a lot of attention right now. That is an in-vitro system often using animal or human cells in culture. They can tell you about a chemical's metabolism and/or interaction — pharmacological or toxicological interaction — with that tissue. And these kinds of technologies are very important.

The point is: which ones are ready today for FDA application? What can we do to improve them, to get them ready for FDA application? That is really where the crux is. It's not so much the development of new technologies, although we do some of that too., but it's really looking at those technologies that are out there and seeing which ones are ready for FDA use. How can we get them ready for FDA use if they're not ready today? So, that's where we spend a lot of our priority and our new budget initiative.

But it's not only important to know what the new technology is, but how to use it. And so, we have one half of our staff who are working on in vitro approaches — like bioinformatic approaches, imaging approaches, approaches using cells in culture, the microphysiological systems, and many other cell-based systems — and then the other half are working on whole animals. A little less than half. We have a lot of people doing pharmacokinetic and biological exposure studies and that kind of thing. But the idea is that we need all these people working together to actually get a full and firm answer.

But the real question about these new technologies is how do they compare to the traditional technologies? How do they compare to what we call the guideline studies? Those studies that have been used by FDA for years now to make critical decisions about compounds and about the safety of compounds. These guidelines studies are the gold standard, and they can then be used to validate, or at least look at the usefulness of these new technologies and so that's one area where we are investing heavily. It's that comparison between the guideline traditional studies and the new technologies, making sure that they're answering the same questions and giving the same answers. That is one area of interest and investment.

The other place is in human capital. There is a funding gap between what it costs today to have an FDA staff member working

here and what it was five or ten years ago. There are inflation costs. There is the normal increase due to the human resources methodology. And of course, there are also contractors. We use quite a few onsite contractors. These aren't contractors that you find in the beltway. These are individuals that work here at NCTR. These are individuals that take care of the animals. The individuals that do a lot of the pathology assessments. So, those individuals, those contractors, those costs unfortunately go up a little bit almost every year. So, if you add it all together you can end up with a real gap in funding between what it takes to maintain your same number of staff today as compared to what it was three, or four, or five years ago. That funding gap is there for the individuals and for the work that's done here every day.

For the work that's done by the NCTR work force, that is one place that we're asking for funds in FY 2022. And then the other area is bioinformatics and artificial intelligence. I told you about the new division that we started about seven years ago, and we're so happy that it has done well. However,, we want to invest more there because it really is an especially critical area for the Agency and for general safety assessment around the world.

And then the last area is food safety. We asked for some additional funds there, and this is really part of the sort of closer to zero thing. Many other things as well, but part of it is close to zero, meaning how can we get foods, especially foods used for children, baby foods, how can we get issues addressed. Such as arsenic levels, lead levels, mercury levels, and mixtures of those. The question about mixtures is really complex but one that we need to address. And so, that's the other area for expansion, the food-safety area.

Those are the four areas that we've asked for additional funding. And it really is important that we are able to obtain those funds. It's in the current President's budget. We hope it's going to be approved. That would really make a big difference for us and allow us to stay on top of these issues.

So, let me sort of move on a bit here with another area. I cannot help but mention our COVID-related studies. We have well over 20 studies in progress now. Some of them have already resulted in publications coming out. This is really an important area of expansion for us, and we also are getting some supplemental money to help in that area as well. We want to keep that going. One of the projects that we're doing is about what sort of viral

components are in wastewater? It can be correlated against the clinical issues that are observed in the regional hospitals and communities. How many people are in the hospital? How many are sick? So, you can take your epidemiology data, combine it with wastewater viral data that tell you about how much COVID-19 may be responsible, and you can start to make assessments. You can start to see trends. And that's what we're interested in. It's possible that you may start to see trends in certain communities either before or as the hospitalization rate is going up. And, you can watch the correlation also go back down again hopefully.

The idea is to stay on top of this to be able to respond more rapidly to new variants that may come along. So, that's one project we're working on, just as an example.

And another one really has to do with, "how do you select the best drugs that could be repurposed?" Often antivirals, as you know, are repurposed to fight and to be useful in therapy against COVID-19 infection, and that process can be augmented using artificial intelligence. And that's what we're doing. We're developing algorithms that allow for enhancing selection of the best drug candidates to go forward for further review because of their attributes and how they could be useful for fighting COVID-19 infection. We have already published in this area and we want to do more to help select those winners for the future that could be antivirals that are useful for repurposing to fight COVID-19.

So, I'll finish up this section by saying that we have a lot of important things to do, and we want to do more in all these areas.

I think it is important here to think about issues such as hiring and recruitment. This is an issue across all the sciences right now. It is truly difficult to recruit and hire individuals and, of course, we want the best and brightest at NCTR and FDA in general. So, one way to do that is to help with the pipeline. We have an undergraduate student summer program here. It's a 10-week intensive course. It's very competitive. We usually get 200 to 300 applications and only take 25 or 30 students, but they get an intense 10-week mentorship by our great mentors here, our NCTR researchers. The students develop projects, complete them, and present them before they go back to usually their university or their professional school. The goal is to keep them in the sciences and hopefully to get them interested in doing research. Maybe some of them will go on to earn their Ph.D. or master's degree. Others may

enter the workforce through the clinical side. But the point is to keep them in the sciences and healthcare.

The other thing we do is we train pre- and post-doctoral students. We use a contract opportunity, the Oak Ridge Associated Universities or ORISE program. We contract with them to provide these students — most already have their PhDs, so, these are post-doctoral fellows. And we support them to do research, and they are really key to NCTR. They're the ones that really get much of the work done here for this campus. And each division of NCTR usually has four or five or more of these post-doctoral fellows. So the ORISE program is key along with our staff fellows that come up within the GS kind of approach. These students, if you will, are key to FDA moving forward. Not only key to getting the work done here, but for training them so that they can either stay at NCTR or they can go to other parts of FDA. Often they go to industry or other government agencies. They can go to the university systems. I've had the privilege of training many of these post-doctoral fellows over the years that have worked with me, and it is key to getting not only your work done but getting them trained up. And some of them, I'm so pleased to say, have gone on to be active in not only FDA, but in some cases they working in other parts of the world. The idea is that they continue to be creative, and add to our science space, and help us. Many of them have been working right here within other parts of FDA since they got their training here at NCTR. So, I'm very, very proud of that student program. As a matter of fact, we have what we call our "wall of fame" which has the names of over 1,300 individuals who have trained here, and it keeps growing each year — by about 100 or each year or two. The idea is that it indicates the amount of training that's done here of individuals that carry on the spirit of FDA, and also the knowledge of what they gained here at NCTR.

So, I'll just finish up here with my opening comments, if that's okay. And part of this idea is what we can do about funding for the future, and I think that there are certain research areas that are key. We've already talked about some of these being the biomarker component and the need to validate these new emerging technologies and make sure that they're going to be useful to FDA. And one way to do that is to compare the emerging technologies against the guideline studies to make sure they work.

The other thing is the perinatal area. NCTR developed the Perinatal Health Center of Excellence (PHCE). At this particular

Center of Excellence perinatal health is a key element in that it really focuses on pregnancy, neonates, and also preemies, early childhood all the way to advanced childhood, and adolescence. And so it takes on an entire area of development and it provides funding for individuals that do research within FDA on that topic. One of the principles of this Center of Excellence is to enhance the opportunity for centers to work together. That is, to get scientists from C working with a scientist from C or C or NCTR. And so, we make sure that people come together and share knowledge and also train along the way, individuals that can carry this on. So this particular program, for which we were very fortunate in 2019 to get funding in our base to augment and support we'd really like to see it expanded now because we're getting large numbers of applications/proposals to do good work within the FDA in the perinatal area. However, we don't have enough funding to fund them all so we just select the very, very best but many go unfunded. We'd like to fund more research projects within the PHCE in the future. another area within perinatal health is rare diseases because, unfortunately, a lot of rare diseases fall in this perinatal area of either newborns or children. We'd like to see more resources go there. FDA has been blessed with some resources to do clinical studies in the area, but we'd like to see additional funding to support product development for rare diseases —research on developing those new agents they have a chance to make it to clinical trials. That is, you have to do the fundamental work first. You have to look at the pharmacokinetics and metabolism. You have to look at the exposure. You have to look at whether or not the agent is safe based on animal model, and in-vitro studies

cells and culture, or both. And then if they pass all that you can see how they may be getting enough support where they can get into clinical trials. But that initial work — Dr. Janet Woodcock usually called it a portion of the critical path —because that early part of the critical path where you're talking about the usual animal cell-culture work that needs to be augmented and supported so that we have enough agents moving through into clinical trials, and possibly forward from there. So we'd like to see more support there.

And another area is nanotechnology. Probably all of you are aware that the actual lipid that allows the vaccines to get into the cells for vaccinating people against COVID-19, those particular message RNAs actually associated within nano-lipid particles. That is an

example of nanotechnology's importance from our perspective and we do have a really good core facility here for nanotoxicology and nanotechnology. It is managed by NCTR and ORA and is available to all of FDA and to other government agencies. The Nanocore is where the nanotoxicology and technology research is done and this area is really expanding. There have been hundreds of applications come in that used nanomaterials. Everything from nanomaterials including some metals to nanomaterials including lipids. But many others as well. And now we have the issue of nano- and micro-plastics that has become an area of interest for the whole world, but also to the FDA. These can be examined in our facility. It's top-notch. It's available for all of FDA to use, and it's right here on the NCTR campus that we share and developed with ORA, which has a big laboratory here as well at the Jefferson Labs campus. We would like to see the Nanocore expanded to be able to do more work in this area.

And then finally is the whole area of pandemic preparedness. This really is a topic of concern right now. Are we ready if we have another viral situation like COVID-19? One way to be ready for that, one of the ingredients that you need are level-three laboratories. These are biosafety level-3 laboratories that will allow us to work with the virus, a live virus. We do not have these kinds of facilities here at NCTR and we desperately need them so that we can work with the virus. And so it's important for level-3 labs to be here so that we can share them with all the other FDA centers and ORA. It is also a great location because we've got those 500 acres that are owned and operated by FDA. It's pretty easy to put up a building and it has to be at level-3 quality so we can do the work we need to do and be prepared for the next pandemic. Those are some of the suggestions there.

So, I'll round out my comments at this point in time. And I'm hoping that perhaps Ron and Steve and others may have a few questions that might be important for me to answer.

Ron Bartek:

Well, I'll take the first crack at that. First of all, Dr. Slikker, terrific presentation. I think Steven and I would readily agree we have so much appreciation for the importance of the work that you and the Center do. I was ready to get a little bit more appreciation of that, but I wasn't fully prepared to experience the excitement that your comments have created in me about not only the importance of your work but the immediacy of the importance of that work, especially in terms of how you are already constantly helping the

other Centers do the important work. And the meshing of important project and [inaudible 00:41:55], of course, lights up my screen.

So, let me just explore that a little bit further. First of all, really impressive examples you gave us of how you are in advance of getting projects with the other centers, and getting their full support, **and** that going forward with those projects you get about 60% participation from the other Centers. That's just magnificent. Mind you, I'd like to take the next step though and ask you, you concluded with tremendous importance of the work you're doing on a daily basis that I bet don't answer neatly when designing a project six months in advance and getting buy-in. And you gave that example of how Janet Woodcock as the CDER director called and said what can we do right away in terms of anesthetics – safety of anesthetics in children. And you jumped on it. Can you help us understand a little bit more about the day-to-day, almost continuous work you must be doing with the other centers? In terms of, you used an example of toxicology. For example, I know you reviewed divisions in neurotoxicology. They have some expertise in toxicology, but I would hope that they're constantly consulting your team on such things, and, as you put it, getting the pre-clinical work done so that these agents are prepared for successful clinical trials. So, I'll stop that long winded question there. But just really impressive.

Dr. William Slikker: Ron, thank you very much. Well, let me say that at any one time, and maybe I said this already, we have between 200 and 250 of these projects going. It takes an incredibly sophisticated computerized pathway to go through all those steps. You could imagine an initial proposal not only through the concept phase and getting the review back from the other centers and them being either pushed aside or augmented to fit the needs. Then, it goes through complete development. Usually, these run 20 to 30 pages but then there are another 20, 30, sometimes 40 pages if it is an animal-use protocol or human-use protocol. All of that has to be done on top of the availability of chemistry and compound-purity data for an a guideline study where you have to do step-by-step verification of everything. If it is an initial study where you're not using the guideline approach but you're developing a whole new technology, there are many questions that come up, and all those are part of our protocol-review system which is a computer-automated system that has all the different abilities to make sure each person has evaluated safety, HR, budget, of course, animal-

use if it's that, or human-use if it's that. And so, all these steps are automated so that you know where you are at in the process..

And then we have a document tracking system that starts from the initial submission of the manuscript as it's going through review by the division and signed off by the division director. Then the manuscript goes into the NCTR-wide review, where it is evaluated by people outside that division and sometimes other people within other parts of the Agency. And of course, if they have co-authors, which there are in some large percentage- of these manuscripts.t then has to be reviewed by the other FDA centers as well **as possible non-FDA authors to** get clearance. all this review process is automated and tracked.

So, we keep track of where the project is and then it gets finally submitted to the journal and you've got to follow that along until the successful completion and actual publication. We couldn't do that without these automated systems. I mentioned that we have a long history in dealing with computer science, but it has been critical because a lot of these systems — like the two I just mentioned — are developed right here in house and we share them with the other FDA Centers. Some have picked them up, and some haven't but they are necessary for us. And therefore, we can share this technology and do it in such a way where it's relatively inexpensive to create. We understand them fully and we can update them when necessary, and those are attributes that you really need with software packages of this type. So, anyway, I hope that sort of answers the question about how we track these studies. Now, getting to the idea of developing agents for treating rare diseases and/or neurotoxic rare diseases. This is a critically important area that's very much in pursuit.

As you know, unfortunately, only about 10% of agents that are currently prescribed to children are actually approved by FDA for that use. They're approved for something else, but the doctor takes on the responsibility of using that in the case of the child and that means that we have to do much better there. We have to not only develop better agents and test better agents, but then we have to work through the review process in clearance of these for use in children. Now we are working on ways to get women, of course, and pregnant women or pregnant people into clinical trials. Then you really do have the opportunity to get the data you need.

But before those clinical trials you need to have the data from the

animal models and from the cell-culture models and that's what we want to emphasize. We want to emphasize that the new technologies rely heavily on biomarkers. I don't know if I mentioned this but there has been a real advance in liquid biomarkers — biomarkers in blood or CSF [cerebral spinal fluid] or urine. FDA has approved the use of a biomarker, actually two, for use by clinicians to determine whether or not they need to do a CT or not for a patient that has sustained a head injury. That is, if you have a head injury and you see a clinician, he's looking at you, looking at your eyeballs, asking you questions, trying to figure out does this person need a CT to make sure that they're not having a problem within the nervous system or are they fine and we don't have to do that? Now they can take a blood sample and they can look and see how much GFAP is in there, and they can make a determination that, "Oh yeah, this person definitely has an indicator or biomarker in the blood that suggests there is a head injury" or when you have a leaky blood-brain barrier some point. and GFAP is coming out of the nervous system and, therefore, we need to go forward with the CT or not depending on what the outcome is. So, these are things that are moving forward. We need to have a lot more of those. We need to develop a lot more of those trusted biomarkers, and we need to use them to help what really is becoming precision medicine where you're really getting the right agent to the right person at the right time. And then the same thing can be done in the cancer arena, where you can follow these markers, different forms of DNA, for example, in the plasma, and determine whether or not your drug therapy or treatment of that cancer is moving you in the right direction or has the cancer changed as it sometimes does. And now there's another sort of cancer that you've got to treat. These biomarkers can tell you that. And so, it will allow the clinician to adapt the therapy to that patient at that time. And that precision medicine is coming our way. We just need to do a lot more work in it to complete that circle.

Ron Bartek: Thank you and I'm really glad that we decided with you to record this session because we'll going back in this recording many times to read everything. So, thank you.

Steven Grossman: Let me encourage people to offer their questions. We have one question; I'll ask that in a second. If we have anybody else from the audience has questions, now is the time to get in the Q&A. And I'm going to set at most 10 minutes, maybe try to do somewhat of a lightening round here. So, let me start with the audience question.

I have a couple others that I hope are answerable in paragraphs. Do you have a team working on evaluating the impact of the health of microplastics in food, such as salmon?

Dr. William Slikker: Well, we don't want to get ahead of ourselves here. There are a lot of steps to really understand about microplastics and nanoplastics. And it is a concern, but what we don't know right now, unfortunately, is how to measure nanomaterial like nanoplastics in food samples. We're starting to learn. We have made some progress but the analytical tools for nanomaterials in real products is not where it needs to be yet. So, first you have to do some basic analytical chemistry, and often it won't work necessarily if you're just doing an LC/MS check. That's not enough. You have to use a whole bunch of other experimentation, which we have in our Nanocore, but you have to apply it appropriately to answer those questions. So, we're working with people in other parts of FDA and around the world on this issue of the analytical methodologies.

Then the next step is to use that approved methodology to really look at exposure. That is, what is in the salmon, in this case? And then of course the next question is going to be, is any of what is in the salmon getting into you and me? Is it going to get into the human? And so, that would be another step. And you do a lot of animal work in there to make sure you understand how to apply those technologies look at the pharmacokinetics. What are the peak periods of exposure if there is exposure? And then go after **the safety issue**. So, we do a lot of that and that needs to be done for the nanoplastics at this point in time. We have a way to go yet before we're able then to hopefully ask the question, is any of that in the human or animal, is any of that producing toxicity And that will be the final step. So, we have a lot of steps to go through to get to that answer, but it is an important one, and the whole world is starting to focus on it.

Steven Grossman: Ron, if you wouldn't mind. I'd like to take the next question.

Ron Bartek: Please.

Steven Grossman: Probably most of the audience has never worked or interacted with NCTR. What are the opportunities for companies, consumers, patients, and trade groups to become involved with NCTR projects?

Dr. William Slikker: Well, you know that's a really good question. And we do have a

lot of interactions, as I mentioned, with universities and with other government agencies. And there we have certain tools that we use, certain instruments. One of them is called the Cooperative Research and Development Agreement (CRADA), and we have done those with industry before, for example. And so, you can use that particular approach to allow you to work together. And it sort of defines what the industry is going to do, what the U.S. Government is going to do, and how they're going to work together to get that done, and what resources are going to be applied to get that work done. And so, it's 17 pages of boiler plate followed by the important part about what you're actually going to do together. But the point is, there is a mechanism. And there are other ones as well. But the idea is that we do have the capability of doing that. Now, we also have the capability of forming public-private partnerships, and we formed one of these over 10 years ago to address the issue of the safe use of anesthetics in children — it's called SmartTots and it really has to do with the coming together on this issue. and linking up as a public-private partner with FDA to advance this area and also to find funding which they've been able to do through donations and other means to fund research in this area of looking for the safe use of anesthetics in children. So, those are just two examples. And so, this can be done if you work at it.

Steven Grossman: Okay, thank you. Ron, I think we may be down to two more questions. And then we'll be on the hour. So, why don't you get the next one, if you have one.

Ron Bartek: Yeah. I'd like to take that opportunity to pursue what you just heard from Dr. Slikker. And that is, do you foresee the possibility of a handful at least of patient advocacy organizations like ours collaborating with the Center, as we do often with CDER for example. And to provide the patient perspective and maybe even some patient samples as you described working for biomarkers and in your sampling animals and people.

Most of our patient advocacy organizations now are really eager to and well-experienced with that kind of collaboration in providing enthusiastic support from patients to provide whatever it is that you and your investigators need to proceed through your work. So, I don't know if your public-private partnership and in scientific societies you mentioned included that kind of effort. But I know we have widespread wholesale collaboration from any number of patient advocacy organizations, if you thought that would be

helpful to your work.

Dr. William Slikker: Well, certainly I think that the CRADA (cooperative research and development agreements) could be one mechanism to do that. There may be more, and we have an office that evaluates what the need is and then how you might be able to meet that. But basically, if the tool is available to other centers, it can be available to NCTR as well. So, if you're using it within the FDA then it should be something that we could adapt and use within NCTR. That's a simple answer. Often, of course as you know, it's more complex than that. But there are also the broad agency announcements (BAAs) that have been available for the last several years. They also allow for a coordination between groups. And that's another way of doing this. But we find interaction with other groups, as we have a lot of interaction with clinical centers because although we have many different animal models and cells in culture on this campus, we do not have human patients that we can work with. So, that's where we have to link with the universities and why my appointment with the University Arkansas for Medical Sciences is so important. But many others around the world and across the United States link up so we can do clinical work as well as getting clinical samples that we can then analyze for biomarkers. So, we should be able to work something out. If other parts of the FDA are doing it, we can do it.

Steven Grossman: I would just add to that [inaudible 00:57:52] a lot of the patient advocacy organizations like ours have all kinds of pre-clinical and translation tools. We have our own animal models. We have our own cell models. And mortician repositories, human cells. So, there might be a good way to help you develop those tools before you can share them with the other Centers.

Dr. William Slikker: That's right. Exactly. So, I like what you're thinking.

Ron Bartek: All right. I'd like to take the privilege of the last question. We're already just a bit over but you said that would be okay. The idea that you have 250 odd projects going at one time is just dizzying. So, I'm going to ask you to do what nobody – you never want to have happen. I want you to pick your favorite trial. Years from now, which is the one of those 250 odd projects that you think is the one that we'll still be talking about still making a dent in the world?

Dr. William Slikker: Oh man. Oh, that's a good question and a difficult one at that. Oh

boy, there are so many. I have to think about those models that use human or animal cells in culture that then can be used to predict what studies you may want to do in the future. And I think those have great power. So, their biomarker-based to some extent, and they're multi-species consistent because you can use it in cells, in animals, and in humans. And they allow you to move across from the pre-clinical or non-clinical range into the clinical setting. So, those are the kinds of things I think that can have the largest impact.

Now, how do you get there? Well, you can get there in part through AI, **bioinformatics**, and computer simulation. You can get there in part through general biology. You can get there from pharmacology and toxicology. You need all of those components really to make it work. So, I think those kinds of projects are key. And one that we're doing now is with HESI (Health and Environmental Sciences Institute). I think you all know who HESI is. It is one of those groups that reaches across industry, government and academics and pulls them together and they're helping us — and have for the last several years — look at those fluid biomarkers of neurotoxicity. And that is really, I think an example where we can take it to the next level. Not only can we confirm that neurotoxic endpoints exist by using neuropathology and supplementing that with imaging where you can see things in a longitudinal fashion in the same animal, same human over time but then looking at the fluid biomarkers that tell you that there is something going amiss with the nervous system. Now, I think this area is one where we have few biomarkers and we need more. It's going to help us unravel some of the mysteries of the nervous system, especially when it comes to assessing toxicity. So, I would say that one has a high chance of great success in the future.

Steven Grossman: Okay, Ron. I think it's yours to wrap up. But thanks to Dr. Slikker.

Ron Bartek: And I'll just add my gratitude and that of our whole organization. And all of our guests today, Dr. Slikker. Just a terrific presentation. And very thoughtful responses to our questions. And we look forward to increasing the collaboration with. I mean that genuinely. I'd like to figure out ways in which our organizations and our members can help you and your center get its very important work done, and knowing that the bottom line is that it gets back to our patients. So, thank you very much for your time today, and the time and energy you've devoted to the center, going back about 15 years now and even before. So, thank you again for

all that you've already done and all that you continue to do. We really deeply appreciate your input today. So.

Dr. William Slikker: Well, I appreciate that Ron and Steve. To both of you, thank you very much. And any time that you can get more people interested in solving a problem, the better. So, thanks very much for the opportunity.

Ron Bartek: Thank you.

Steven Grossman: Thank you. And I –

Dr. William Slikker: Take care.

Steven Grossman: You too.

[End of Audio]

Duration: 63 minutes