SCIENCE BOARD TO THE FOOD AND DRUG ADMINISTRATION

ADVISORY COMMITTEE MEETING

Monday, October 7, 2019

8:30 a.m.

U.S. Food and Drug Administration

Building 31

10903 New Hampshire Avenue

Silver Spring, Maryland 20993

PARTICIPANTS

BOARD MEMBERS:

MARK R. MCLELLAN, PH.D., CHAIR

RAKESH RAGHUWANSHI, MPH, DESIGNATED FEDERAL OFFICER

CYNTHIA A. AFSHARI, PH.D., DABT

ANTHONY BAHINSKI, PH.D., M.B.A, FAHA

KATHYRN BOOR, PH.D.

BARBARA B. KOWALCYK, PH.D.

RICHARD LINTON, PH.D.

LISA K. NOLAN, D.V.M., M.S., PH.D. [VIA PHONE]

THEODORE F. REISS, M.D., M.B.E.

DOJIN RYU, PH.D.

MINNIE SARWAL, M.D., D.C.H. MRCP, PH.D. [VIA PHONE]

SCOTT J.S. STEELE, PH.D.

LAURA L. TOSI, M.D.

CONNIE WEAVER, PH.D.

XIANG-QUN (SEAN) XIE, PH.D., EMBA

A G E N D A

A G E N D A (CONTINUED)

P R O C E E D I N G S

(8:38 a.m.)

CHAIRMAN MCLELLAN: Good morning. And welcome to the Science Board for the Food and Drug Administration. My name is Mark McClellan. I'd like to start off with a reminder that if you take your technology out and tell it to be quiet, that would be appreciated. If you can't tell it to be quiet, then turn it off. Okay.

We have a full day and lots to do, so I'll officially now call the Science Board meeting to order. We'd like to start by going around and introducing ourselves. For those of you who are old hats, you'll know that as we desire to speak, one of the things we do is put our flag up like this and that way I'm able to identify you and call on you to speak. Otherwise we'll be looking for an engaged conversation. For those of you who are on the phone, we'll be asking you to simply interrupt us and I'll do my best to catch you.

So, if you would, let's go ahead and start and introduce yourselves. Those of you who are new,

tell us just a little bit more about yourself, okay?

Thanks.

DR. REISS: So I guess I'll start it. I'm not new. Ted Reese, head of Clinical Research and Development at Celgene and I&I

DR. STEELE: I'm Scott Steele at the University of Rochester, associate professor in Public Health Sciences and I direct our regulatory science programs.

DR. TOSI: Laura Tosi, and I'm at Children's Hospital in George Washington University and I run our Bone Health Program at Children's Hospital.

DR. BOOR: Kathyrn Boor and I am new. I am Dean of the College of Agriculture and Life Sciences at Cornell University and my background is as a molecular biologist focused on food safety.

DR. WEAVER: I'm Connie Weaver. I'm a Distinguished Professor Emerita at Purdue University in Food Science and Human Nutrition.

DR. RYU: My name is Dojin Ryu. I'm Interim Director of the School of Food Science and also I'm new. My background is mold and mycotoxins, or broadly

defined as chemical food safety.

DR. AFSHARI: Cindy Afshari. I'm a Lead Nonclinical Safety at Janssen Pharmaceutical.

DR. LINTON: Good morning. Rich Linton. I'm also a new person on the committee. I'm Dean at the College of Agriculture and Life Sciences at NC State University. My background is as a food scientist, a food microbiologist, a bacteriologist by training.

DR. BAHINSKI: Hi. Tony Bahinski. I'm Global Head of Safety Pharmacology at GlaxoSmithKline.

DR. XIE: Good morning. My name is Sean Xie. I'm a Professor of Pharmaceutical Science and Associate Dean for Research Innovation. Also, I run a NIDA-funded Center of Excellence for Computational Drug Abuse Research.

DR. KOWALCYK: Barb Kowalcyk. I'm faculty at the Ohio State University in the Department of Food Science. My background is epidemiology and biostatistics and food safety.

CHAIRMAN MCLELLAN: So as you can tell, these things, you need to somewhat bring them close

and speak clearly. So I am Mark McClellan. Let's see. At last note, I am now at the University of North Texas. That's an inside joke. And I'm the Vice President for Research and Innovation there.

MR. RAGHUWANSHI: Morning. I'm Rakesh Raghuwanshi, Designated Federal Officer for the Science Board.

RADM HINTON: Good morning, Denise Hinton, FDA's Chief Scientist.

DR. ABERNETHY: Good morning. Amy Abernethy, principal deputy commissioner and Acting Chief Information Officer at FDA.

DR. KEEFE: Good morning. I'm Dennis Keith. I'm the Director of the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition.

DR. MAYNE: Good morning. I'm Susan Mayne and I direct the Center for Food Safety and Applied Nutrition. And welcome to the new members.

DR. MARKS: I'm Peter Marks, Director of the Center for Biologics Evaluation and Research. And also welcome. Thanks.

DR. WILSON: Good morning Caroline Wilson,

Associate Director for Research in the Center for Biologics.

DR. TAN: Good morning. I'm Regina Tan and I'm the new Director for the Office of Research for the Center for Veterinary Medicine.

I come here from the Department of Agriculture where I was the Director for the Office of Food Safety and I'm a proud graduate of Purdue University.

DR. MENDRICK: Hi, I'm Donna Mendrick. I'm the Associate Director of Regulatory Activities from NCTR.

CHAIRMAN MCLELLAN: Very good. And so, Rich and Sean and Kathyrn, thank you, particularly the three of you for joining us. I think you'll find our discussions enjoyable learning and really an opportunity to give back if you would, to our government and be a part of that science discussion for the future.

We always start our conversation with a reminder of conflict of interest and so for that I'll turn it over to Rakesh.

MR. RAGHUWANSHI: Yes, so good morning once again. Welcome to all of you. Thank you for traveling from near and far to be here. And thanks to the new members for your willingness to serve. Also welcome to the members of the public who are here and have an interest in today's topic. Today the Science Board will hear a response from CBER to the recommendations the Board made in 2017 as they reviewed CBER’s research program.

The Science Board will also discuss color additives and behavioral effects in children. All members of this advisory committee are special government employees and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to those found at 18 USC 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws.

Based on the agenda for today's meeting, no conflict of interest waivers have been issued. We have one open public comment period scheduled for 10:00 a.m. with two members of the public having requested to speak.

And once again for our Science Board members on the phone, we'll give you a chance to introduce yourselves a momentarily. Please remember to unmute your phone when you're speaking and mute your phone when you're not speaking.

If you're logged into the webcast, the link was sent to you this morning. Just make sure to turn down your computer speakers.

And for those of you at the table again, please make sure you speak very clearly into the microphone so our transcriber can duly record everything.

CHAIRMAN MCLELLAN: So let's go to the telephone lines and for those of you on the lines, we'd give you an opportunity here to please introduce yourselves.

DR. NOLAN: Lisa Nolan, Dean of the College

of Veterinary Medicine at the University of Georgia.

CHAIRMAN MCLELLAN: Thank you Lisa. Minnie?

DR. SARWAL: Minnie Sarwal, Professor of Surgery, Medicine and Pediatrics at the University of California, San Francisco, Director of Precision Transplant Medicine and the Kidney Pancreas Transplant Program.

CHAIRMAN MCLELLAN: Thank you, Lisa. Thank you, Minnie. And thank you for taking the time to dial in if you couldn't be here, to dial in and join us. We appreciate that.

So our flow of the meeting today will be pretty standard. As we get into some of these areas my intention will be to pull out a lot of discussion. I will be particularly looking for your opinions in terms of many of the challenges that we'll end up getting into. I'm trying to position us as a resource at this time for FDA to use your varying opinions, and we hope you will have varying opinions, as a feedback to them to assess next steps and where they need to go.

I do not necessarily expect this to come to

a sense of momentous decision, but rather an engaged conversation, engaged discussion that brings your expertise to the table and integrates it with the issues at hand. But to start, let's go to our chief scientist's update and move on to Denise. Thank you for being here so much.

RADM HINTON: Thank you. I appreciate it. Good morning and thank you to all of our Science Board members for traveling to be here with us today. And then for those of you on the phone, we thank you for your time and commitment as well. I'd like to welcome Dr. Boor, Dr. Linton, and Dr. Ryu as our new members of the Science Board. We are grateful for your service. Thank you.

I would like to give you some highlights of the work we've been doing in the Office of the Chief Scientist over the course of the year. We are fresh off of hosting our 2019 Science Forum, which was a two-day event showcasing research efforts of our scientists. It attracted a global audience. We had almost 1700 participants and 267 posters over eight different topics of interest.

A few days prior to that we had our seventh annual Scientific Computing Days focused on areas such as artificial intelligence, genomics, and modeling and simulation. This drew over 1,000 attendees and featured a digital poster session which was piloted and highly lauded by our attendees.

I mentioned these two events because supporting our scientists is one of my top priorities and then last fiscal year we put on 32 training events for almost 4,000 participants and awarded over 1,600 continuing education units. Interestingly, in 83 percent of the CE evaluation respondents reported there was an impact of CE on their competence and this addressed their knowledge gaps.

It's important to me that our scientists and reviewers stay at the forefront of science. Our office funded 28 intramural grants in areas including medical countermeasures, nanotechnology, diagnostics, clinical trial enhancements, and antimicrobial resistance, among others.

We also completed 12 cooperative research and development agreements, we call CRADAs, including

one with the National Institute for Innovation and Manufacturing Biopharmaceuticals, or NIIMBL. This is the Manufacturing USA public-private partnership. This agreement enables FDA and NIIMBL to support pre-competitive research, development, testing and training needed to foster advanced manufacturing innovations in areas such as continuous manufacturing, on demand manufacturing and advanced process control technologies amongst others. Ultimately advances in these areas will help increase NIIMBL's national impact by enhancing patient access to new and improved medicines.

More broadly, FDA is working with several Manufacturing USA institutes to assist their efforts and to identify gaps in technology, understand the key factors for bringing 21st Century technologies to the market and to strengthen the workforce and training.

I mentioned medical countermeasures earlier and recently we just issued three extramural contracts under the fiscal year 2019 broad agency announcement. And this is to advance the regulatory science needed to further medical countermeasure development for

Acute Radiation Syndrome, Ebola virus, and Zika. We continue to work closely with the Department of Defense to help expedite the development and availability of medical products necessary to support the unique needs of our military personnel.

In August this year, FDA granted a variance request and this was submitted by the Army Blood Program for the use of cold stored platelets in theater for DOD personnel.

In addition to speaking to partnerships, we continue to work with our CERSI at Yale and Mayo Clinic and worked on three collaborative projects and this was aimed at reducing harm for opioid addiction and abuse, which is a top priority for the Commissioner and Principal Deputy Commissioner of this agency.

I also want to say that I'm proud that this year we also spearheaded an Overdose and Naloxone Administration training course using didactic and practical skills and we've already trained over 2,500 people in this area.

Our Office of Laboratory Safety is also

involved in similar efforts and they developed an online training to train personnel in opioid exposure and Naloxone use.

I'll end by congratulating our Health Informatics staff, which created and continues to develop Precision FDA. This is a virtual laboratory for analysis of data sets by scientists both inside and outside of the FDA. Precision FDA received the 2019 Federal IT Innovation Award and we're proud of those who made that possible.

In closing, I'd like to make a point to say this whenever I can, that I'm very proud of our scientists here at the FDA, our researchers and our review staff and the dedication that they have to our mission every day. Our agency is truly science-based and I am amazed at how focused our professionals are on the daily work.

Through changes in administrations, changes in leadership, changes in political climate, there's one thing that doesn't change and that is the diligence and steady hand of the FDA workforce that keeps us as the gold standard of product regulation.

It's an honor to support and represent them at various meetings, including this one. If you know any talented scientists interested in medical product regulation or public health, I encourage you to point them over towards FDA.

Thank you all once again for your time, your service and your thoughts, ideas and opinions, and I look forward to a productive session today. Thank you.

CHAIRMAN MCLELLAN: Thank you Denise. I think if it's okay with you, we'll also include Amy's report and then maybe the Board might have some questions for the two of you. Is that all right?

RADM HINTON: Absolutely.

CHAIRMAN MCLELLAN: So we're very happy to have any Abernethy here is the Principal Deputy Commissioner and appreciate you taking time to join us.

DR. ABERNETHY: Thank you. I'm honored to be here with you and I want to echo Denise's welcome and most sincere thanks for those of you here for the Science Board, those on the phone and participating

and a huge thanks for taking the time out of your busy schedules to spend time with us. Your input is really important to advancing the work that we all do together.

For those of you don't know me, as just mentioned, my name's Amy Abernethy. I'm the Principal Deputy Commissioner and also the Acting Chief Information Officer. I am a hematologist-oncologist as well as a palliative medicine physician. I came here by way of previously being a Professor of Medicine at Duke. I was there for 20 years. And then also the tech industry, including being at a small tech startup and on the board of large technical companies as well.

And what I learned during that time was that FDA helps to set the regulations, which really are the guideposts and help us understand what to do and what not to do. So especially we can focus on that which is going to move us all forward and not get distracted on activities that might not be as impactful. And so, your advice about how we do work going forward is pretty critical.

One of the areas that we'll talk about later today is that I'm particularly involved in FDA's technical efforts, including our recently announced Technology Modernization Action Plan, which is a step towards modernizing FDA's approach to the use of technology for regulatory missions, including the review of medical product applications. We call this the TMAP. And this is intended to provide a sturdy technological foundation for the development of our ongoing strategy around how we use data itself, including our strategy for stewardship, security, quality control, analysis, and real time use of data. And it's going into it really accelerate our path to better therapeutic and diagnostic options for patients and the community at large.

We also include in this action plan, modernization of FDA's infrastructure to make sure that we can support, for example, the use of emerging technologies and capabilities such as artificial intelligence, blockchain, and other solutions. And we're going to be ramping up activities that modernize how we use tech and work with the stakeholder

community. We'll be talking about this after the Scientific Board later today in a more informal session. And I look forward to getting your feedback.

And so, I'm going to focus my prepared comments on other areas of modernization and innovation here at FDA, including the area of food safety.

As part of FDA's new era of smarter food safety, the FDA is exploring the potential for artificial intelligence, AI, to improve screening of imported food before it's allowed in the United States for sale to US customers and it's example of where we're going. We use import screening and actually use a tool that we call PREDICT or otherwise known as the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting. Now you see why we call it PREDICT.

And PREDICT helps FDA employees speed their review of import entries while targeting the products most likely to be at risk for evaluation. This tool is intended to help us automatically search and analyze large amounts of current and historical data

and it helps FDA personnel identify patterns, flag issues, and determine the potential risk of new shipments in real time. The increased number of automated decisions give human reviewers more time to focus on high risk entries, as you can imagine, and it's a very valuable tool in ensuring food safety of imported food in the United States.

In a proof of concept project, PREDICT will serve as a testing comparator as FDA develops a prototype machine learning model to identify imported seafood shipments that are more likely to be violative. We expect that machine learning will improve the sensitivity, specificity, and predictive value of the selection model for import review. And this will allow us to understand how machine learning and other types of capabilities can help us update what we do every day, but do so in a way that's scientifically based, comparing prior tools to updated tools incorporating machine learning.

And the other area of focus, as Denise previously mentioned, it's the opioid crisis. This is a top agency priority and it touches on so many of the

different kinds of work that FDA does as an agency, from social science, informed decisions about consumer information and labeling, to product chemistry and formulation, to law enforcement and stopping illegal drugs in transit.

We continue to work to support the development of an access to drugs, medical devices, digital health technologies, and diagnostic tests that can offer solutions, detecting, treating and preventing opioid use disorder, addressing diversion, and treating pain.

In order to reduce overall opioid deaths FDA is working to increase the availability of Naloxone. As Denise mentioned, this is an emergency opioid overdose treatment. Making Naloxone more wildly available in every pharmacy as an approved over-the-counter product is an important public health goal as we see it.

To encourage drug companies to enter the OTC market, the FDA designed, tested, and validated key portions of the labeling needed for OTC Naloxone products. This year, FDA also approved the first

generic nasal Naloxone product. There are prioritized pathway for products that treat emergency overdoses and we see all of these different kinds of solutions coming together as the way of bringing innovation to areas like a public health crisis like the opioid story.

We also play a vital role in helping to stop the illicit drugs that continue to come into our country often through the mail. Another area of particular concern is the illegal sale of prescription opioids online through rogue internet pharmacies, social media, and even the Dark Net. In many cases, products illegally marketed online as opioids are counterfeit drugs that contain potentially lethal doses of illicit compounds like fentanyl. Just two milligrams of fentanyl can be lethal.

Recent government data show a leveling off or a slight decrease in the number of deaths attributed to opioids and we want to ensure FDA continues to pursue policies that are effective in reducing opioid morbidity and mortality and proactively identifying ways to better address the

opioid misuse and abuse and respond to new challenges in this manner. For example, on the tech side, we're also looking at how we can bring technology modernization into our international mail facilities to better detect drugs at risk in partnership with the Customs and Border Protection.

Now moving to another, a critical area of public health concern. Vaping. Vaping illness continues to be an area of concern to us all. The FDA and the US CDC are working tirelessly to investigate the distressing incidents of severe respiratory illness associated with vaping products. FDA and CDC are currently working closely with state and local health officials to investigate these incidents as quickly as possible and we are committed to taking appropriate actions as a clearer picture of the facts emerge.

To help gather and analyze as much information as possible, the FDA's laboratory is working closely with our federal and state partners to identify the products or substances that may be causing the illnesses. FDA is analyzing samples

submitted by a number of states for the presence of a broad range of chemicals including nicotine, THC, and other cannabinoids along with cutting agents, diluents, and other additives: pesticides, opioids, poisons, heavy metals, and toxics. That's a lot.

FDA remains committed to improving public health and there are many priority issues and concerns. And as you can see, this also means in huge amounts of data that we need to process today and also in the future and we want to make sure we're continuously prepared.

As you can see as FDA working together with the Science Board, we want to do the best together for public health and we thank you for being here with us today and let's get on to the meeting at hand.

CHAIRMAN MCLELLAN: Thank you. I hope you guys are willing to maybe answer any questions or comments real quick. Does the Board have any comments on the reports we've just heard? Barb.

DR. KOWALCYK: Barbara Kowalcyk. Thank you for the updates and I was really particularly happy to hear about FDA's TMAP, the Technology Modernization

Action Plan, I think is what it stands for.

Okay. so I just wanted to ask you a quick question about that. There's been several committee reports from this Board that have identified IT issues and the ability to share data within FDA and across the various partners with FDA.

I'm thinking particularly of a report that I chaired couple of years ago looking at the ability of some of the food safety laboratories, your state partners, to be able to upload data into FDA directly and there were some challenges around that.
So I was wondering if you could just expand a little bit on how broad TMAP will be and will it be looking at ways to better facilitate sharing from your external partners?

DR. ABERNETHY: This is a great question. So when I came to FDA, really data and technology was one of my key areas of focus on that brought me here. And I was expecting to want to need to work on data sharing as one of the critical areas. And I was also expecting the predominant issue to be essentially, you know, motivating people to be willing to share,

thinking about the contractual and confidential information management issues, et cetera.

And what I discovered was that practically speaking, we needed to deal with some critical technology issues first. So the reason that the TMAP is structured in the way that it is, first focused on technological capabilities and then subsequently on what can we do both within the agency but also the biomedical and food community overall, is because it's clear that being able to use data better, including data sharing within FDA and across government is going to require us to have the technical capabilities to allow us to do so.

Denise mentioned Precision FDA in her opening remarks, which is a really useful example, a pilot, as well as what I would call a use case that shows what it looks like when we can create collaborative data sharing environments where multiple scientists, regulators and others can actually see the same datasets and develop algorithms off those datasets, cross check each other's work, and also do new work. And so, we know that there's the ability to

do that, but we actually have to make sure that we build those technical environments and then also, essentially the muscle of now how to share capabilities in the future.

CHAIRMAN MCLELLAN: Yes, Cynthia.

DR. AFSHARI: Thank you very much for your updates. Quite a lot going on and certainly with so many changing dynamics, it's nice to see you continuing to steer the ship.

In particular Dr. Hinton, I wanted to congratulate you on the Science symposia and the data science activities and they sound like they drew quite a crowd.

I wanted to ask you at the end of your talk, you talked about, you know, continued desire to draw scientists into FDA and for us to make recommendations. And I know as a Board we've also focused over the past few years around talent development, retention, recruiting.

I'm just wondering how that's going. And how you, you know, certainly as things are more rapidly evolving with machine learning and artificial

intelligence, it means sometimes you have to reach even broader than just scientists and biologists, but also into computer science and engineering. And so I was wondering if you could provide an update on how that's going.

RADM HINTON: I will and then Dr. Abernethy will join in. And one of the things we continue to look for and recruit, you know, probably the best scientists that we can and that includes researchers and those that have support missions as well as in project management and the like, with our Office of Talent Solutions and which we're working closely with.

We are continuing to progress as far as the hiring goes. We have seen a trajectory in our hiring as far as biologists, chemists, and the like across the board. We have a direct hiring mechanism for a number of those positions and those are, of course, through USA Jobs. So we continue to try to frame out and direct and look for those direct hiring certs that fit the position that we have at hand. And I think more currently to-date are those that have the background and the expertise to address our vaping

issues.

So I think we've made considerable progress to-date. I'm sorry I don't have the exact numbers, but I think the trajectory is good. So I think we are confident that as we continue to work closely with OTS and OHR that we will be able to bring on the talent that's needed.

And then, with regards to hiring those within the data scientists and the data analytics and the machine learning where they vary very differently. That's why we have our Acting Chief Information Officer here to help shape out the position descriptions and the unique needs in those areas.

DR. ABERNETHY: And I'll add something, and I think Dr. Marks also might have some comments as it relates to hiring.

As Denise mentioned certainly we have a number of initiatives in place to hire more scientists. We also are starting to ramp up our use of the Cures hiring authority which came with the Cures bill. And within the technical side, we now have a direct hire authority for 2210, which is for

our engineering and analytic capabilities.

That being said, I think that we can all acknowledge that, especially in the data and technology space, there are many more needs than there really are people readily prepared to do this work. And we acknowledge FDA, not only do we need to hire, but we also need to be thoughtful about different ways of solving this problem, including new ways of working together with scientists, including through our CERSI program. So Denise mentioned that. As well as unlocking the cognitive elasticity that already exists within FDA.

So how do we train and build people inside of FDA to be data scientists of the future? And so, that's one of the things that we're thinking about.

From my perspective, I think we have to actually put all of the capabilities on the table and ask how we're going to do this differently going forward.

Dr. Marks, anything to add?

DR. MARKS: I basically would agree and I think it's clearly a challenge to recruit and retain

the highest caliber scientists within the agency. And that's not just because of the salary issue. It's because right now it's an incredibly competitive environment that we're working in. When you think about it, with a number of venture capital gene therapy startups, cell therapy groups, antisense companies we are competing for top talent at leading edge areas where there's a lot of competition.

The same thing goes with data sciences. In fact, there's seems to be a large company moving in across the river and in Virginia that might be a competitive for peoplefor the FDA. So we'll continue to work on that.

I think it is through the Cures authority, the Cures hiring authority is very helpful. And additionally, I think our ability to articulate a compelling reason to participate in what we do here at FDA is helpful. So we'll work together with that, but I'm not going to sugar coat it. It's a challenge. And we will rise to the challenge, I hope.

CHAIRMAN MCLELLAN: Thank you. Tony, you will be our last comment before moving on. Thank you.

DR. BAHINSKI: All right, thank you. I'm really heartened to hear about the technologies moving forward and the progress that you've made. It maybe a bit of an esoteric question, but you know, the reactions, you know, tend to for crises or, you know, issues tend to be more reactive than perspective in looking forward down.

I was wondering if there's any efforts at the FDA with, you know, as you're hiring these new people, using artificial intelligence to kind of get ahead of the curve and kind of sort of, you know, a way to predict, you know, what are the upcoming issues. I know there's a lot of ways you leverage that with experts including the Science Board to kind of look prospectively down the road. But are you thinking about that at all or is that a way beyond kind of where you are right now?

DR. ABERNETHY: So actually we're thinking about it in two ways right now, but I would love advice about how to continue to think more creatively in the future.

Two examples of what we're doing right now.

Now that we're starting to be able to gather data and look at it differently inside the agency, we're also looking at what does that tell us about where, for example scientific direction is moving and what we need to be thinking about. And that's very early, but we actually have intentionally started to look at the data from that perspective.

Secondarily, what we see is that the book of work of the agency, itself, is accelerating. So if we look at the number of gene therapy applications coming into CBER, if we look at the potential of having now multiple reviews per medical product, if we look at just the distribution of work happening on the food safety side, and the book of the work in the agency is accelerating at a pace that we're still trying to describe, but we think is something north of 10X and probably south of a 100X, but real. And we're actually, we've got a book of work right now trying to figure out the math.

That's important because it tells us that we actually have to think about how do we bring in tools and solutions to do our work as efficiently as

possible and potentially differently in the future in order to accommodate that kind of difference between now and 20 years from now. Those are the first two things that we're working on. But we, I'd love additional advice and I'm sure Dr. Marks has other thoughts.

DR. MARKS: So I just want to just say that, you know, I think each of the centers has a group, they may call it something differently. Ours, it's the Medical Countermeasures and Emerging Threats Group, that basically their job is to lay awake at night and worry about what's coming down.

And so, whether it be the misuse of genome editing technology or the intentional release of some virus into any type of environmental source. We do have people that think about that. We also have you know, we work together with the Department. There are groups that work together and as part of a Health and Human Services that have exercises to prepare for potential threats, be they a novel influenza strain that could be a pandemic, or other, you know, rad new type threats, other things. I know that the foods

folks do similar things. The vet med people -- so each of the centers have their own way of doing this.

The final thing I'd say is that we're also -- just to bring technology into this in terms of the looking for things that could happen adversely to products that are out there. We are looking into using our artificial intelligence. We have a contract right now in place with at our center with IBM Watson and others to try to use artificial intelligence to essentially pick through data to figure out signals by using natural language processing and AI.

So just among some of the things that are being done.

CHAIRMAN MCLELLAN: Thank you all. And committee members, thank you for engaging -- you're watching in live there, the engagement based on prior review studies and coming forward with what's happening as a follow on. I love that. I think that's exactly what we want to see for the future.

So speaking of prior reviews, back in 2017, we established a review of CBER’s research program a couple of years back and it was led by a number of

members of our Board here. And so, we're in a great position now to be a welcoming Peter Marks, our Director and Carolyn Wilson, our Associate Director to hear feedback on that review. I look forward to hearing an update.

Carolyn, it looks like you're taking the mic.

DR. WILSON: Yes, I am.

Good morning and thank you. I'm pleased to be here and as you noted, Dr. Marks is here as well to respond to Qs and As as we go along.

So this was a review that was done a few years ago and I'm grateful to have the opportunity to be here today to present to you the work we've done to respond to the many very constructive recommendations that we received from that review. Let's see. So to remind you, let's see. Next slide.

Okay. So to remind you of the charge to the Science Board and the subcommittee of the Science Board. We had four major areas and it was a fairly broad remit because we asked the subcommittee to really review the entire center and how our scientific

endeavors support our regulatory mission, to also make specific recommendations of how we could address through our portfolio -- through changes in our portfolio to accomplish our regulatory and public health mission, identified gaps in regulatory science capabilities or expertise, and such as opportunities for collaborations to better leverage our ongoing programs.

And I do want to mention I didn't include a slide of the subcommittee members, but there are still four members of the current Board who participated in the subcommittee and that is Tony Bahinksi, Cindy Afshari, Scott Steele, and Ted Reiss. So I'm really grateful that they're still on the Board to hear this report back from the center so you can hear the outcome of the hard work you did.

So our major find the major findings and overall conclusions were strong research program that supports our regulatory mission, that we use a researcher reviewer model that in an extraordinarily effective way to address our needs, that the external research collaborations help respond to emerging

regulatory challenges that we use core facilities to support research in our center and other centers and that overall have outstanding programs that we've cultivated and that continued growth of these programs will ensure success in the future.

So of course we were very pleased to have an overall positive report, but of course they didn't stop there or else I'd be able to sit down, but they also went on to give us a number of center-wide recommendations, as well as office specific recommendations. So I'm going to go through this in a fair amount of detail and I apologize, it's a little bit tedious. But I felt that to do due justice to the many recommendations that we receive from the Board that this was our, the best way to do it. So I'm just going to dive right in here.

So in the area of setting research priorities and providing a nimble scientific infrastructure, they recommend that we develop a strategic research plan with mix of intramural and extramural collaborations to address those needs. So we are in the process right now developing a new

strategic plan for the center. One of the four goals in that strategic plan is around the Regulatory Science Program and we're incorporating the advice from these recommendations into our planning process.

And I also am happy to report, in the past two years we've significantly expanded our extramural collaborations. We developed an SOP for engaging with public-private partnerships. We've actually implemented new agreements in the past year and are in the process of evaluating another one right now. And we anticipate this part of our program portfolio to continue to grow. We also have significantly expanded the use of the broad agency announcement and the CERSI programs. Next slide.

In particular we've done a lot to advertise and educate staff about these mechanisms. We developed an internet site with help from Carol Linden and her staff to provide a much more detailed information about the resources and how to engage in using the BAA and CERSI mechanisms.

We provided training to our regulatory science council, which for those of you who aren't

familiar, that is our governance board that oversees our research programs. It's composed of the center director, the deputy, myself as well as all the office directors and their deputies and the office specific associate directors for research.

And in FY ’19, we actually funded nine broad agency announcements and seven CERSI research collaborations. And I'll just, as a footnote mention that there were a couple of the CERSI collaborations that actually did involve engaging youth, developing methodology using AI to look through healthcare data.

So continuing then. The next recommendation in this area was to develop a center-wide horizon scanning process. And in FY ‘19, we actually use the Regulatory Science Council to perform this center-wide horizon scanning. We identified high priority new needs within each office and then also looked at cross-cutting issues that would really support everybody. And as you can imagine in today's world, a very high priority was expanding our capacity in bioinformatics, computational biology, and included in that really is also artificial intelligence. And this

is really to support not just the research enterprise, but also to engage these tools to support the review process. Next slide.

And the third recommendation in this topic is to develop a more nimble and adaptive governance structure and culture using the Regulatory Science Council and the Resource Committee to develop contingency plans to shift resources and projects rapidly.

And so, one of the things that the center has done over the past couple of years is really mature a process that we were using previously. But I think that we've gotten much better at it. And that's called an unfunded needs process to allocate funding, really starting as early as the second quarter of each fiscal year, looking at fallout money for example from FTE under burn or other large projects that maybe are not coming in, in terms of contracts is as expensive as initially estimated, and trying to go through a list that the offices provide at the beginning of the year, but also as issues arise mid-year this provides for a way to reallocate those funds that become

available throughout the year and put them into our high priority needs.

So we feel that we also address this by trying to use user fee funds now to fund projects that are directly supporting regulatory review. And that also frees up budget authority, which is a funding mechanism that is much more flexible than user fees and allows us to have a little bit more nimbleness in our resource allocation.

And finally, we also do keep some money in reserves. Both Dr. Marks and myself each have a little chunk that allows us to also fund urgent needs at any point in the year. So next slide.

So the next major bucket that the committee report talks about is in research collaborations. The first recommendation there is to further expand collaborations and personnel exchanges with a variety of agencies addressing similar emerging areas. And we do that through collaborations in workshops. So in FY '18, we had a collaboration with NIH to have a workshop on the science and regulation of life, microbiome-based products used to prevent treat or

cure in humans. And in FY ‘19 we also had a workshop on biomarkers to advanced development of preventive vaccines, which was also done with NIH.

We also have ongoing discussions as Dr. Marks mentioned with all of these different government agencies to identify emerging areas of need and to try to be proactive in developing those.

The next area, which was increased engagement in public-private partnerships. I already mentioned. We have really moved forward in doing that in the past year or two. And then, additional workshops. We've also been leveraging the CERSI program. And in October of last year it was actually a joint CBER-CDER workshop that was held and leveraged the expertise in several of the CERSIs to look at predictive immunogenicity for better clinical outcomes. Next slide.

The next major bucket is researcher viewer model and one of the recommendations was to designate protected time for research. So I'm going to take a moment here because this one is a very difficult one to implement. Because our researchers do have all the

same responsibilities as fulltime review scientists, which means they have their own portfolio of regulatory files that they are responsible for because of their specific expertise as new BLAs, INDs, and so on, come in they may be the best person in the office to address that particular regulatory file.

And because the regulatory workload is somewhat stochastic, if you will, in the sense that we never know when a new IND or -- BLAs are a little bit more predictable, but even those, you never know for sure. And so, this is something that while we realize it is obviously a very important goal and we tried to do it when feasible, we can't really carve out and guarantee this for every single research staff. Next slide.

Okay. There we go. So then the next area was on training, professional development and future workforce.

I think it went two slides now. Can you go back? Oh, okay. No, I don't know what happened there. Okay. This is really strange. Do you see what's happening on the screen? Yeah. Okay. Oh,

there. Sorry. Okay. So there we go.

So in this area exchanges and rotation opportunities should include not only other parts of FDA, academia, and other agencies also have bi-directional exchanges and a sabbatical program. So there is a mechanism to support this recommendation and it's called the Intergovernmental Personnel Act, which allows civilian federal employees to serve with others, state, local government, universities, or other eligible organizations up to two years without losing employee rights or benefits.

And likewise, employees from other eligible organizations may serve at federal agencies. So this is logistically possible from the point of view of a legal framework to support it. But again, we come back to the same issue that I mentioned on the last slide, which is with the regulatory workload of our researcher viewers, this may be a very difficult one to implement, and so it's going to have to be addressed on a case-by-case basis.

Again, we recognize the value of being able to go to another institution to learn new methodology

and refresh your skillset, but it's just a big challenge for us. Next slide.

Also in training professional development and future workforce, assuring appropriate travel funding. We think this may have, we're not exactly sure, but we think this may have been perhaps a misunderstanding of our current system where we actually do provide resources to every staff member to support travel. It's called a Continuing Education Account. In addition, each office and division is really very supportive in allocating operating funds sufficient to support travel to at least one meeting per year, per staff. Many of our research scientists also often get additional grants, either from the Office of Chief Scientist through their various funding mechanisms or other external entities. And they may be able to tap into using those funds to also support travel of their staff or their fellows.

So we think that we are doing a pretty good job in this area. Obviously there's always a desire to travel more to hear more about what's going on. But we, as a center, clearly recognize the importance

and value of being able to get to at least scientific or professional meeting in your field to ensure you remain up-to-date. And likewise, to provide an opportunity for us to share the research we're doing here with the external community.

The second is to expand mentorship and professional development. And we have developed in the past year what we call a scientific mentoring tips document that’s specific for research staff at all levels and has various information that's specific to the mentor and the mentee. And we're hoping that that will help to create and foster that culture around scientific mentoring.

We also have expanded what we used to call our PI Peer Mentoring Group, so now it's called PI Networking Group. And that actually is really turning into a fantastic resource for the research PIs to come once a month and just share among each other how they're dealing with the challenges of the environment that they're in. And a number of really good recommendations and questions and concerns have risen out of that group to my level. So it's working both

ways in helping them at the peer level, but also bubbling up issues that are -- that require some attention from my perspective. Next slide.

Impact and sustainability of core facilities. The recommendation was to provide necessary resources with sustainable funding models, including how they could be shared more broadly within the FDA. So the Regulatory Science Council last year developed a new funding model for core facilities. We actually it developed in FY ‘18 and phased it in, in ‘18 and implemented it in ‘19.

And the idea is, is that what we do is in the recognition that the core facilities are providing an important role in supporting all of the research within the center. We have a mixed model of central funding. So we use our general account to fund approximately half of all the core facility funding needs. But then we distribute the other funding as to each office as it's proportional to the usage. And we think that that's an important element because it creates a sense of accountability and transparency to the offices, the divisions and the PIs. We actually

report out on a quarterly basis all the usage statistics down to the PI level so that people can be aware that, you know, these aren't really free. There is a cost to them. But also again, you know, making sure that we continue to support them in and manner that's fair.

We've also implemented a new contracting mechanism using the IDIIQ, which is indefinite quantity -- indefinite delivery, indefinite quantity. Thank you. To allow for use of what we call a self-insurance approach to support equipment repair. So, for example, this year we put some money that fell out at the end of the year into this IDIQ to make it available to support equipment repair on an ongoing needs in FY ‘20. And that allows us for some of the equipment like, say a tabletop centrifuge and things like that, that tend to not be particularly cost effective to put in a expensive preventive maintenance agreement and breaks down very rarely.

This is a more cost effective approach to, to meeting those needs. So that actually has been met with a lot of enthusiasm and this also allows for

preventive maintenance visits, but not a preventive maintenance contract. So you can sort of gauge the amount of preventative maintenance that you may need for a specific type of equipment, which again tends to be a better deal than the vendor PM contracts. Next slide.

Okay. I'm going to pause there because I went through a lot of information before I dive into the offices, to see if there's any questions or if people are happier that I just keep going. I can do it either way. What would you like?

CHAIRMAN MCLELLAN: I'm sure Carolyn we'll have some questions. This is great.

DR. WILSON: Okay, I'll keep going --

CHAIRMAN MCLELLAN: The flags are all up. So Connie why don't we start with you?

DR. WEAVER: So I was really curious about your live microbiome-based product priority. I was at an annual Bone and Mineral Science meeting a week ago, and what I saw in probiotics associated with bone, it looks to me like there's nothing systematic. They just take whatever combination of live organisms in

whatever doses and just try it.

DR. WILSON: So this is -- I may be better off leaving this to Dr. Marks to address. Okay. So, the challenge with probiotics is that if there's not a specific claim to treat or mitigate disease, then it's a food supplement, and so some of that is not regulated.

Then depending on how the language around how it's being used. We get into the probiotics space or what we call live Biotherapeutics when there's an intention to treat, mitigate, or cure disease, and then they need to come in and it has to be under IND. And then, obviously we work with the sponsors to make sure that it is done in a rigorous clinical trial setting and so on and so forth.

Peter, did you want to add anything to that?

DR. MARKS: No. What you're looking at is one of the challenges here that many people try to use over-the-counter preparations without -- in essentially for prevention, treatment cure, mitigation of disease without having to come in for an investigation of new drug application, which creates

this issue that they tend to study complex mixtures.

We have groups that are trying to sort through this and they're trying to look at what individual strains of bacteria will do. And it's pretty clear that as it would make sense that different strains of bacteria might have different effects. So we'll see more work in this area. There's not much we can do to shut some of this down without, you know, without doing a lot of detective work.

CHAIRMAN MCLELLAN: We'll go to Ted, then Cynthia, then Scott. Ted.

DR. REISS: Well first of all, we'd just like to thank you guys for all the work that you've done here. It was really just a tremendous interaction. We really sort of enjoyed working with you guys on the strategic plan.

I just want to circle back to the, actually the question that was asked before to maybe just pull out a few additional subtleties. In one of the things that we talked about was the horizon scanning sort of issues and then the -- you know, cross-collaboration

with other department -- other agencies of the government.

So can you give us just a little bit of sense of perhaps how that horizon scanning, whether it's the look at what's coming in, what's new on the horizon or what threats might be on the horizon. And the conversations you might be having with, you know, with the CDC, DOD and so on and so forth. Is that part of the process now?

DR. WILSON: So the process that was used within, so this was sort of a bottom-up process. So it started within Offices and Divisions and really tapping into the collective expertise and knowledge of the researchers as well as the review staff looking at, you know, what are they hearing about at scientific meetings? You know, just what are they seeing developing in their fields of research and integrating that with what's likely to turn into medical products and they think are going to be challenges that would face, they would be facing.

And then, they developed from that a number of issues that they identified as sort of some of it's

as, as Donna Mendrick knows, who chairs the Emerging Sciences Working Group.

We've identified what we call emerging science, which is really things that haven't hit our doors yet or just barely starting to touch us and more several years away versus evolving science, which are things that are already in-house perhaps or clearly hitting our doors, but it's moving very rapidly. So you can imagine there's quite a lot of things, especially in our space between things like genome editing and what we were just talking about, therapeutic products and so on.

So a lot of the topics that bubbled up from those conversations were what I would call in the evolving science. So there are things that are already ongoing and we have some element of research facing them, but maybe there's more that we need to do to really be able to address all of the scientific challenges that those bring. And then identifying things that are more gaps where we really don't have anything. And when I get into the office specific recommendations, you'll see some new hires that we've

brought on to address some of those gaps, for example.

I think that answers your question.

DR. REISS: Just to follow up. Any cross-fertilization with other agencies or the government around that?

DR. WILSON: Right. So that's happening more at the agency level. I mean, well I should say within the offices and the center, there's always ongoing dialogue with CDC and DOD and HHS and those conversations are happening all the time in a variety of different topics. But what I was going to say is, again, at the agency level, this Emerging Science Working Group that Donna chairs, we've actually brought in systematically, representatives from a variety of different government agencies, including NSF for example, in addition to places like DOD and CDC and others to try to get a handle on what do they see as sort of the emerging technologies that may not be on our radar quite yet.

And then, as the representative from that agency-wide group, I can also bring that back to the center, the things that I think are important.

DR. REISS: Good. Thank you.

CHAIRMAN MCLELLAN: Thank you. Cynthia.

DR. AFSHARI: Thank you Carolyn. I just, again, wanted to commend the CBER leadership for addressing the comments in the original review and just how far you've come. You know, I think seeing things around the unfunded model and the self-insurance just as an example of how to achieve additional value out of existing resources. My question was you know, certainly sitting on the committee, we felt what was really strong in the first point you addressed, which is the reviewer regulator model. It's unique in CBER and I think the committee felt like it was very, very strong and really is necessary given the mission of the division.

You know, as we've heard already though, there's increasing complexity to the products that you're seeing and also an acceleration of volume. And so I'm wondering, because you mentioned it a couple of times, some of the things that the committee brought up as important to kind of solidify and maintain that ability, you know, such as protecting time for

research.

I'm wondering, given the challenges that you talked about with the volume and the lack of predictivity for what's coming in this increasing complexity, do you see a threat to that model that you may eventually end up in a place where you have to have dedicated reviewers who don't have time for research? And is there anything we could do as a committee to help address that?

DR. WILSON: So it’s important to note that we have fulltime review staff and researcher reviewers work in tandem with fulltime reviewers. So there is a very big effort thanks to 21st Century Cures and other resources that are coming into the agency to beef up our expertise and our personnel in the really critical areas, especially in the Office of Tissues and Advanced Therapies.

And so, that while right now there's a big burden on the researcher reviewers, we hope in the next couple years that it'll start to normalize back to where it was before as these new reviewers get up to speed and you know, get hired, get up to speed.

Obviously, you don't walk in the door and do a BLA, but, you know, it's a transition period right now and there is a big burden on the researchers, but I don't think that there's ever any intention to go away from that model. I think the center is really committed to that being a very important model.

CHAIRMAN MCLELLAN: Scott.

DR. STEELE: Thank you. Thanks, Carolyn. I also want to echo my thanks. I appreciate the thorough responses and the number of activities going on. It's really exciting. You answered some of my questions on the horizon scanning.

I was just wondering if that's going to be a reoccurring activity --

DR. WILSON: Yes.

DR. STEELE: One other question, but go ahead.

DR. WILSON: So what we decided in conjunction with the Regulatory Science Council, they felt that doing it every year was maybe a little too frequent. So I think we landed with every four years.

But in addition to the horizon scanning,

what we also do is every year one office does a programmatic review and that's doing a deeper dive within the office to look at, you know, how's their research portfolio meeting their objectives and goals? Are there gaps in their portfolio?

And so, that is sort of a little bit of an office-specific horizon scanning that will continue to also bubble up issues that need to be addressed. And that the way that works is we have four offices, so it's one every year. So each office once every four years. So that's going on as a cycle in addition to a center-wide horizon review.

I welcome your thoughts if you think that's a good approach.

DR. STEELE: It seems like a great approach. Thank you.

DR. WILSON: Great.

DR. STEELE: The other question was following up on the exchanges and recognizing the challenges with having people, you know, participate in those exchanges. But I was just wondering if even since a number of agencies do them, if a shorter, you

know, 30, 60 day type of TDY is still an opportunity that could be beneficial, but not be a significant burden.

And then the other piece is, using that to bring in people from DOD, NIST, if that's something you've been utilizing or you see value in or if agencies are willing to do that?

DR. WILSON: So we have on occasion allowed individuals to go on for relatively short, I call them mini-sabbaticals, to collaborating research universities. And then, we have not formally looked at bringing in members of other agencies in a systematic way. But again, there are a number of occasions when our research scientists will bring in a person from another collaborating institution to learn a technique or to teach them a technique and so on. So, so there is this going on at sort of a low level, but not in a systematic way.

DR. STEELE: Thank you.

DR. WILSON: Okay. I'm going to push on. Oh, is there one more question? Sorry.

CHAIRMAN MCLELLAN: We have one more. Go

ahead Sean.

DR. XIE: It's very nice to hear how the is project going.

But I tried to follow Ted’s comments. So one of the things that’s going -- you and the Chief Scientist also mentioned modernize the FDA -- the product review processing regulatory -- by implementing AI. But Peter also says this is a competitive at the hiring people. I think this is true because in academic, for example, my lab and my center has been going for 25 years for example, focused on cannabinoid and chemical genomics platform. It's integrated with the GPU machine and deep learning and all integrates together.

So I was thinking a good, you mentioned that also intramural and extramural model, a program going. So I serve on the NIH study section once in awhile they come up with a program project so it would be much faster for FDA to adapt other that is already established for different projects and use it for your CBER-related recreation processes.

Those are more cost efficient because if

you’re were hiring new people to do the from the beginning, it will take awhile. But yeah, so I don't know what is in this aspect prospect --

DR. WILSON: So I’ll make several comments on that. I think obviously as you point out, we are leveraging external capabilities and expertise through external collaborations both through the broad agency announcement and the CERSI. Those are more around and methods development and leveraging methods that have been developed and those institutions. But it's important to note that obviously also we have regulatory data and so we can't do everything through an external partnership. But to the extent that we can harness that external knowledge to develop the methods that then we could bring in-house to, to support our needs as you point out that that is an approach we're taking.

The second thing I will also mention in terms of internal expertise, this year we stood up an Artificial Intelligence Working Group and lady of the day, Donna Mendrick, is also chairing that she hardly ever sleeps. And that that has been a great resource

for the scientists within the agency.

It turns out there's actually quite a lot of work already going on in the agency that's using the tools of AI or understand AI, like in Center for Devices, to be able to evaluate regulatory devices and learning from those regulatory reviews. And so, this is a great forum for the scientists to come in, learn from each other and it's another way of leveraging the expertise in-house.

And then finally, that group is also looking at and discussing an internal training program to try to augment the expertise that we have here. And I think either Amy or Denise also mentioned the idea of, you know, trying to further those skill development in-house.

All right. If there's no other questions, cause there is actually quite a bit more to go and maybe I won't pause for questions. I'll just get to the end cause otherwise we may run out of time.

So I'm going to go through the office specific recommendations. Just to remind you, there's four different offices that each have a research

component. And this is not in any particular order other than alphabetical.

So Office of Biostatistics and Epidemiology. The first recommendation is talking about AI and natural language processing, and I think I've already mentioned that a lot of this. So you know, again, we've been leveraging the best contract, BAA, and also the CERSI mechanism to really augment our abilities in these areas.

Upgrading technology. We weren't quite sure exactly what this referred to, but we do think that we're using the cutting edge technologies in the HIVE, which as you may recall is the highly integrated virtual environment that is supporting next generation sequencing analysis. But it also can support other things we're looking at whether or not that may be a tool to help support AI activities.

And then we also do a lot of innovative modeling and simulation. And then the data mining of electronic health records sources, patient input elicitation and others. So next slide.

At the time of this review, there was quite

a lot of expertise and personnel gaps and OBE has really done a lot to reduce personnel vacancies over the past year. For example, medical officer or reviewer vacancies were reduced by 30 percent. And again, to address these expertise gaps, they're really looking at bringing in staff who have new skills such as understanding how to harness real world evidence, using developing tools to support science-based patient input, the Sentinel Initiative, innovative clinical trials, which again is a very big piece of 21st Century Cures Act, as well as model informed drug development. Next slide.

So the next recommendation is to competitive to ensure there's time to advance regulatory science and do interesting research and the funding to support that. So in the Office of Biostatistics and Epidemiology, they don't necessarily have the same researcher reviewer model that we have in the lab-based programs, but they do support postdoctoral fellows and then those individuals do nothing but research. They don't do review. And they're really bringing in the new knowledge to apply modeling

computational science and develop analytic approaches that the office needs. They also do a lot of methods development through the Public Health Surveillance Authority and again through a variety of different external efforts such as BEST and Sentinel.

The next is to travel to conferences, to present research findings and develop contacts with other researchers. And again, we recognize that this is a really critically important thing that the office needs to support. Again, we think that the office has really emphasized providing staff with opportunities to present and attend scientific meetings throughout the year and to support professional development for physicians. So we're not quite sure what more we can do here, but we think -- we certainly agree with the committee that this is a critically important activity to support.

Office of Blood Research and Review. It was noted that additional resources could be productively allocated for the focus generation of high throughput sequencing data for generation of high -- for generating reference panels for blood group and then

HLA antigens. And it was also noted that various NIH supported large scale human genome sequencing programs should be leveraged for data to inform these efforts and offices looking at how to increase resources for high throughput sequencing to support reference panel development as well as furthering collaborations with NIH to support this endeavor. Next slide.

Collaborations with industry were recommended as well as academic partners to accelerate some of these efforts and limit the costs and suggested that they may need to upgrade technology and hire a new FTE with relevant skills. So BR is currently looking at outside partnerships as appropriate to accelerate the effort and limit the cost in this area. But at this time we don't have anything specific to report. And while resources are always a challenge. We obviously are taking this recommendation into account and looking at our overall programmatic priorities within the office to see whether or not an FTE can be dedicated to this area.

FDA should consider how to best hire and retain promising scientists and other staff,

especially those who are otherwise in high demand such as big data informatics and statistics. And as you, I think we've discussed a lot and as you heard that this is a very top priority for the agency. And obviously the office and the center is working to use the new hiring program for supporting recruitment through 21st Century Cures as that becomes a viable option as well. Next slide.

This is to deploy an additional FTE to expand the ‘omic and bioinformatic expertise for development of disease specificity and toxicity biomarkers for a variety of different target pathogens. And we are leveraging or the office is leveraging the expertise within HIVE to apply bioinformatic expertise and identify newer approaches to develop and evaluate detection assays for emerging infectious diseases in blood donors. Also looking at how to shift programmatic resources through training and direction.

All right. And we'll move on to Office of Tissues and Advanced Therapies. And bear with me because there were a lot of recommendations for this

office, but the bonus is that Office of Vaccines is just one slide, so if you can stick with it, we're getting close to the end when we hit Office of Vaccines.

All right. So add depth in areas covered within the office to anticipate future needs. And we're very excited two PIs were recruited this year. They both have arrived. They started in August. And the first Dr. Pankak Mandal is starting a research program on CRISPR engineered hematopoietic stem cell-based cellular therapies and Dr. Ronit Mazor is starting a research program on immunogenicity of adeno-associated viral vectors. Next slide.

And this is continuing how to expand depth in high priority needs. And as was mentioned, the office has specific areas they identified in their horizon scanning and those include personalized cancer vaccines. And in particular, the computational biology piece where the INDs are coming in using AI-based algorithms to match MHC peptide combinations, and the immunology of antigen processing and presentation is being integrated into all of that.

And this is an area where we really need to increase our understanding of these approaches in order to do a more thorough review.

The other areas, is bioprocessing and advanced manufacturing technologies for cell and gene therapies. As you know, this is an incredibly exciting time in the field, but as you probably know, it's also running into challenges as these licensed products are going into larger scale manufacturing and they're running into capability issues. So this is something that we're hoping we can help address through a combination of intermural research, as well as Denise mentioned, we're also partnering with other external groups such as NIIMBL and Army to be aware of their efforts and provide input there as well. Next slide.

Assuring strategic and budget planning, that appropriate distribution of resources are weighted toward emerging and rapidly evolving areas and that plan should enable flexibility. So I covered the general approaches but also more specifically, in FY ‘19 CBER was grateful to receive new funding authority

to support advanced manufacturing and OTAT was allocated approximately $2 million to support this work.

And about half of that went to support the startup package for Dr. Mandal's program and the other half went to support projects that are ongoing PIs are addressing, which we think will help support advanced manufacturing such as karyotype and chromatin stability in the stem cell arena. Lentiviral vector manufacturing, which is, you know, is still old school transfection of four plasmids. And then human iPSCs, which is a very important area for product development. And how to control differentiation and the genetic engineering of these cells is going to be an important issue to move these into the marketplace.

There was also a recommendation to extend collaborations to other divisions in CBER, and again, we're not quite sure, this may have just been a lack of knowledge in this area, but we actually, this office collaborates quite broadly within the center, so and beyond the center. So there are 84 collaborations with other -- a variety of other

government entities and 57 are within the FDA. And of those more than half, 33, are within CBER but not within the office.

So we think for, you know, the number of staff and the number of projects within that office that this is a fairly, you know, collaborative group, but obviously if there are specific collaborations that you think would augment the research efforts there, we're open to those ideas as well. Next slide.

Another was improving the portfolio for AAV gene therapy. And as I mentioned, we're very excited to have Dr. Ronit Mazor, who joined us in August, who's going to be looking at immunogenicity of AAV vectors, which if you're familiar with that field, I'm sure you know that that has been a real major issue and can often be rate limiting to the clinical success of AAV vector administration. Next slide.

Oh dear. Okay. There's that weird thing happening again. Oh, thank you Rakesh.

Further development of platform technology for enumeration of vector preparations through advanced development of standards or centralized

laboratories. And in this slide, in the next, I'm going to go through some various specific things that we're doing in the standards arena.

I also want to just mention that actually just last week, we, the center led the FDA Standards Day, which is the first time we've come together as an agency and shared the information and knowledge around standard development that we're doing across the different centers. And it was a very exciting opportunity to hear about all the work that we're doing. And what was also interesting to me is that most of the other centers and agency components were not aware of all the work we're doing. And a lot of it is originating in our research laboratories.

So OTAT, and its predecessor Offices of Cell Tissues and Gene Therapies, actually have had a long history of collaborative development of standards for vectors. Actually, I can proudly say I was the person who started this with the first replication competent retrovirus standard that was available through ATCC in the mid-nineties. That was followed by an adenovirus 5 standard. And then, more recently there's been a

lot of work with developing standards for AAV vectors. Standards for aAAV-2 and AAV-8 have been developed and are available through ATCC, OTAT staff planned and held a workshop on dose determining assays last year in December. And there are continuing discussions about the need to generate reference standards for additional strains of AAV. USP is interested and we're continuing to have that dialogue. Next slide.

In addition, there's a lot of work on lentiviral vector reference material. Last March there was a meeting in Norfolk by ISBioTech and that we actually have a reference material that's currently being manufactured at the Montreal National Research Council in Canada, and that that will be shipped to ATCC for vialing and distribution and hopes to be available in spring of 2020.

So we think that we're doing a lot of work there, but again, if you still feel there's specific areas that we need to address better -- I should say that one of the other things that's coming out of 21st Century Cures, as you may know, is a mandate to work with the Standard Development Organization to advanced

development of standards and reference materials for regenerative medicine. And so, there's a lot of work also going on there, which actually isn't mentioned on that slide. But I can answer questions about that if they come up.

Contribute to understanding the potential impact of and improve assays for possible genotoxicity related to CRISPR-CAS9 gene therapy. And I would just say that this is really genome editing writ large.

Dr. Zhaohui Ye is a principal investigator who's evaluating specificity and efficiency of various CRISPR-based editing platforms using high throughput sequencing. And he's doing that through two collaborations. One with an investigator at the National Center for Toxicological Research and another one in collaboration with the UCSFs Stanford CERSI.

In addition, we're also doing studies of CAS9 immunogenicity. Dr Zuben Sauna’s lab is developing assays to identify T-cell epitopes as well as antibody reactivity in clinical samples. And there's a number of strategies that can also be harnessed to reduce the immunogenicity risk of CAS9,

and he's looking into how to how to best address that. Next slide.

Prepare for rapid evolution of stem cell and tissue engineering products, including expanding leadership and expertise in manufacturing controls and accompanying devices. And again, I think that we've addressed that in some of the prior slides where we talked about new recruits and new investments in these areas. Next slide.

Prepare -- okay. We are coming to the end. Next slide.

Office of Vaccines. I promised you it's just the one slide. Strength and ability to attract fellows and OVR accepts this recommendation and they have really worked to attract and retain fellows. However, there are changes that are beyond their control and really beyond the center's control. There's agency-wide issues and policies that have been implemented in the last two to three years that do impact our ability to attract and retain fellows.

One of the things that the agency is doing to hopefully address some but not all of these policy

changes is to stand up an FDA traineeship program. We are hoping for spring of 2020 and that will allow us to have an additional mechanism to the ORISE program, which has been somewhat problematic just because of the need to use an interagency agreement and the challenges of the procurement and acquisition issues in that arena. So having it in-house, we're hoping will alleviate some of those concerns.

The second is there needs to be a continuing recognition that the requirement that investigators can carry out and assay themselves, should not limit consideration of novel techniques being proposed from outside. These techniques should be adopted by FDA investigators if it seems to be useful for their work, but there should not be a requirement for them to do so. And OVR again accepts this recommendation. They thought it was consistent with previous and current policy, but they have reiterated this approach to managers and investigators to make sure that it is clear.

So next slide. It’s just a summary. And again, CBER is grateful for and accepts the major

findings at the center and office levels. As you can see we have implemented almost all recommendations with a few exceptions. Hopefully I've explained to you why and those exceptions are really due to limitations of resources or other restrictions. Next slide.

I just want to finish with another thank you to the Science Board and especially to the subcommittee because it was a very in-depth review. I think it was carried out over the course of about a year with quite a number of telecons, an in-person meeting. And it was as you can see, generated a very constructive report.

I want to thank many staff who supported the implementation of these recommendations, obviously center-wide, but in particular the four office associate directors for research Drs. Atreya, Chumakov, Epstein, and Tiwari. And then, Monica Young and Emily Braunstein who are in my group, who were instrumental in helping to support all of these activities.

So I'll stop there and happy to answer any

additional questions and I'm sorry if I've gone a little long.

CHAIRMAN MCLELLAN: No, it's a very impressive response. And you know, kudos to both the Board team that did that review and the extensive time they gave to it and kudos also to your staff and the way you've responded.

So we have time really for just a question or two and be happy to entertain those if there's any pending.

Scott, go ahead.

DR. STEELE: Maybe just a quick question. Thank you again, Carolyn. Just thinking of other initiatives and alignment with NIH is, are there particular groups involved with the All of Us initiative at NIH? I'm just thinking about some of the work they're doing with the next generation sequencing and the data they're gathering.

DR. WILSON: just so you know, the FDA has a Genomics Working Group and we are having conversations with NHGRI around a variety of topics to encourage synergism and collaboration in that arena. And I

think there are also other sort of agency-wide connections going on. I know Dr. Collins actually gave one of the keynote talks at the FDA Science Symposium and talked about some of the work that's going on. There's sort of an executive level council that is FDA and NIH components where they discuss things at a higher level and a broader initiative.

I don't know, Denise, if you want to add anything to that based on what you see in that arena? Okay.

All alright. Well thank you again.

CHAIRMAN MCLELLAN: So Board members members, I think it's worth saying an extra thanks to Carolyn. Carolyn, if you can't tell, has been a deep resource for us, incredibly well-connected with this Board and engaging and we appreciate that Carolyn. Just a phenomenal connection there.

I particularly want to congratulate you, on a bit of creativity, the IDIQ need approach. I'm going to steal some thinking behind that and I hope you appreciate a lot of our commentary in that review. It was all about maintaining the sharpness and

creativity and broadness of your team. And that was lot of that feedback to tease out that research and the injection of new thinking to the team.

DR. WILSON: Yes, most definitely. And again, we do appreciate it. As you can see, we've really taken all the recommendations to heart.

CHAIRMAN MCLELLAN: Great. And ladies and gentlemen with that, we're going to exercise a bit of a break here and take a recess for 10 minutes and so be back and ready to go. And thank you very much.

(Recess.)

CHAIRMAN MCLELLAN: Okay. I think we will bring ourselves back into regular order and start to move forward.

So we have in our agenda planning for this meeting, we purposely have flipped this portion our agenda in order to quite frankly bring a more diverse thinking onto the table for our Board members to be able to react to as they engage with them, with our public hearing portion as well as with our CFSAN portion of this subject.

So we're now going to conduct our open

public hearing portion of today's meeting and both for the FDA, as well as the public in general. We are passionate and believe in the transparent process of information gathering that this part of the meeting reflects and to ensure that transparency and for the Board, FDA believes it's important that we fully understand the context of individuals presentations. So we'd ask that for that reason that we encourage speakers at the beginning of your oral statements to fully advise the Committee of any financial responsibilities they may have with a company or group that may be effected by the topics of today's meeting.

If you choose not to address this issue of financial relationship, at the beginning of the statement, it will not preclude you from speaking. However, we believe this inappropriate.

And I understand that there are two requests. So we're going to proceed down that list. And the first individual I'll invite to the podium is John Cox from the International Association of Color Manufacturers. John, thank you for coming to speak to the Science Board this morning.

MR. COX: Thank you, Dr. McLellan. Good morning.

Thank you. Good morning. Thank you for the opportunity to provide comments to the Science Board today. I am John Cox, General Counsel to the International Association of Color Manufacturers. Our member companies create and use color additives in a wide variety of foods and beverages. And Dr. McLellan, I hope that satisfies the financial connection.

In the short time that I have today, I'd like to comment on recent risk assessments conducted by various regulatory bodies to help inform the Science Board’s discussion.

Rakesh can you confirm that the Board has received our detailed comments?

MR. RAGHUWANSHI: They have.

MR. COX: Wonderful. So my brief comments today are a summary of our detailed written comments. And in those comments we make three main points. Number one, the latest science does not establish a link between synthetic color additives and ADHD.

Number two, we believe that it is significant that regulatory authorities have recently reconfirmed the safety of these ingredients. And finally, we don't believe that food color exclusion diets are effective as nonpharmacological treatment of children with ADHD and related problem behaviors.

Detailed risk assessments for seven of the nine FDA certified food colors have been conducted by the European Food Safety Authority or the Joint Expert Committee on Food Additives, or both, since the 2011 Food Advisory Committee findings.

EFSA re-evaluated synthetic food colors in the last 10 years is part of its broader food additive re-evaluation program. Six of the FD&C colors are approved for use in Europe. No concerns were raised about safety or exposure and in most cases the previous acceptable daily intakes were retained. JECFA has also re-evaluated seven FD&C colors since 2011. Acceptable daily intakes were developed by conducting risk assessments on each color based on a relevant endpoint of toxicity other than neural behavioral effects.

Both JECFA and EFSA reviewed the McCann-Southampton study that was discussed in detail during the 2011 FDA Food Advisory Committee meeting. EFSA evaluated the study individually and JECFA in the context of its re-evaluations of the relevant colors. Both agencies independently reached the same conclusion as the FDA, that the available data on neural behavioral effects provided insufficient data upon which to base a risk assessment for these effects in children.

Both JECFA and EFSA have concluded that the color additives they've re-evaluated are safe for their intended use in foods and for all users, including children.

One of the questions that the Science Board has been asked to consider today is whether there is a link between consumption of FD&C color additives in food by children from the general population and adverse effects in their behavior. The latest science does not establish a link between consumption of FD&C color additives in food by children from the general population and adverse effects on their behavior.

Reviews of the clinical trial literature associated with ADHD and the consumption of color additives show that any indication of adverse reactions is limited to children who react adversely to foods or are part of a sensitive subpopulation and so have produced neither consistent nor strong association between color additive intake and undesired symptoms including ADHD. It's also worth noting that any reliable effect linking synthetic colors to ADHD symptoms are only present in parent ratings, but not in teacher or observer ratings.

Additionally, animal studies in mice and rats designed to detect neural behavioral effects have been conducted for several food color additives, including the US certified food colors. None of the animal studies were considered to provide robust evidence of behavioral effects and could not be used in the risk assessments of either JECFA or EFSA.

As the Board knows, there was a challenge study that attempted to replicate the findings of the Southampton study in a different population and this was published by Lok and others in 2013. This study

replicated the design of the McCann study in eight to nine year old children in Hong Kong. Lok was part of the McCann research team as a graduate student at Southampton, so she was intimately familiar with the study design. In contrast to the McCann-Southampton study, Lok did not detect an association between color additive intake and behavior.

There were some differences between the studies. Specifically children with ADHD and currently being treated with medication were excluded from the Lok study. The preservative sodium benzoate was not included in the same treatment as food colors, but was tested separately and the administration of the treatment was given in capsules instead of juice. However, we feel that this study warrants close examination to understand why no one has been able to reproduce the findings of the Southampton study.

The second question the Board is asked to consider is whether the latest science establishes that the use of artificial food color exclusions is an efficacious dietary intervention in the nonpharmacological treatment of children with ADHD and

related problem behaviors. Excluding FD&C colors would not be an efficacious dietary intervention.

In fact, a diet excluding FD&C colors has the lowest impact in improving behavior relative to other interventions as noted and multiple meta-analyses. Those that have found a benefit were unable to do so conclusively. Nigg and others in 2012 noted methodological limitations. Stevenson and others in 2014 concluded that the effect size was too small to be of value and the patient population for which an elimination diet would benefit remains uncertain. These authors came to similar conclusions as others before, that the data do not support dietary restriction including the elimination of food color additives as an efficacious treatment for ADHD.

One systematic review, Pelsser and others in 2017, performed a critical analysis of two meta-analyses that evaluated the evidence associated with elimination diets of food colors and ADHD and concluded the results do not support restriction of food colors for the treatment of ADHD. That same study suggests that a few foods diet approach has the

most substantial impact and suggest that this could be a useful treatment for subgroups of children with ADHD.

The most recent review that we have found published in 2019, Cagigal and others, also concluded that there is no clear evidence that supports dietary interventions for the treatment of ADHD.

Your background materials indicate that the Science Board is aware of these studies Nigg, Sonuga-Barke and Stevenson. Taken together the studies all indicate that the potential effectiveness of dietary interventions, including color additive exclusion diets as treatment for ADHD has not been demonstrated. The meta-analysis and systematic reviews published in the last five to seven years coalesce around a common theme that current evidence for dietary methods both restrictive, including color restricting, and pro-nutrient diet diets does not support an association between food colors and neural behavioral endpoints.

So the available studies don't suggest the dietary therapy has a beneficial effect compared to placebo and therefore it can't be recommended as an

evidence-based intervention for ADHD.

Thank you for your attention today. IACM submitted detailed comments to the Board and we support the continued investigation of this issue. Food policy decisions that affect children's health should be based on the best possible scientific evidence.

To-date, the reviews of the clinical trial literature associated with ADHD and the consumption of color additives have produced neither consistent nor strong association between color additive intake and undesired symptoms including ADHD. The results of the Southampton studies have not been reproducible. So far all regulatory reviewers agree that no causal relationship between synthetic colors and ADHD has been established. The color additives industry will continue to participate as regulatory authorities examine this issue, but to-date we don't see a relationship between color additives and any neural behavioral effects.

I would like to thank the Board for the opportunity to speak to you today. I'd also like to

thank my colleagues at IACM, Sarah Codrea and Ms. Maria Bastaki for their help in drafting the comments to the Board. Thank you.

CHAIRMAN MCLELLAN: Thank you Mr. Cox. We appreciate the submission of both the written material and your oral presentation from the Association of Color Manufacturers. Thank you very much.

Next, I'd like to no, we're going to hold questions until we have the full -- I'd like to invite Lisa Lefferts from the Center for Science and Public Interest to come forward. Lisa, thank you for bringing forward your comments to the Board.

DR. LEFFERTS: Thank you very much. It's an honor to be here. My name is Lisa Lefferts. I'm a Senior Scientist with Center for Science in the Public Interest. And to respond to your question we are an independent organization. We don't receive any industry or government grants. I have no other financial interest in this topic.

We are an independent nonprofit science-based health advocacy organization. With over half a million subscribers. And we evaluate the safety of

different additives. We mainly rate most additives as safe, but we do have concerns about this group of additives.

This slide is taken from a presentation that Dr. Chronis-Tuscano made to the Food Advisory Committee in 2011 and I just put it up as a little background to highlight that this is a very serious endpoint. We're talking about, that is associated with lifelong impairment and functioning. Different environmental factors can contribute to the expression, severity course, and comorbid conditions of ADHD. And there's some very serious long-term sequelae.

This is also taken from a slide presentation by Dr. Stevenson that discusses hyperactivity is existing on -- there's a normal distribution of hyperactivity, and children with an extreme degree of hyperactivity may be diagnosed with ADHD. So at the very end of that spectrum. So we're concerned of course, with any environmental factors that could be shifting this distribution. So there you see the extreme degree.

And since 2011, this concept of ADHD as a continuum or spectrum has gained traction. So this is a quote from the associate editor of JAMA Pediatrics in 2016, suggesting that we should move from a diagnosis of ADHD to one of attention deficit hyperactivity spectrum disorder and that the shift should be from treating attentional capacity as a clinical disease to recognizing that we need to do all we can to help children maximize their ability to focus. And similarly, this is taken from a article in from 2019 in Nature Genetics. It was the discovery of the first genome-wide significant risk loci for ADHD and the results of that study encouraged a dimensional view of ADHD as the extreme end of the continuum of symptoms.

So in 2011, this was a taken from the background document provided to the Food Advisory Committee. FDA concluded that a causal relationship between exposure to certified color additives and hyperactivity in children in the general population had not been established. The paper also states that for certain susceptible children with ADHD and other

problem behaviors, however, the data suggests that their condition may be exacerbated by exposure to a number of substances including synthetic color additives.

And I just want to note that FDA did not ask the Food Advisory Committee if color additives are safe. And this is the legal definition of safety for color additives. Safe means that there is convincing evidence that establishes with a reasonable certainty that no harm will result from the intended use of the color additive. And I urge the Board and the agency to consider this and which is a very different standard than establishing a causal relationship.

Also FDA did not ask the advisory committee about this portion of its conclusion that certain susceptible children that their condition can be exacerbated by exposure to synthetic color additives.

In determining safety, the law requires that FDA consider a number of relevant factors including the probable consumption of/or other relevant exposure of the additive in food drugs or devices or cosmetics. And it also requires that the

cumulative effect of such additive be taken into account considering chemically or pharmacologically related substances in the diet.

So the top three food dyes certified for use in food in the United States; Red 40, Yellow 5, and Yellow 6 comprise over 90 percent of the dye certified for use in food and they are all Azo dyes. And there are a number of other Azo dyes that are approved by FDA for use in drugs and cosmetics. And I've listed those here. So these are all chemically related, but the cumulative effect has not been taken into account.

Now in Europe. The presence of any of those three dyes triggers a label requirement and this is what it looks like. It says that the dyes may have an adverse effect on attention and activity in children.

As I mentioned in the previous, or almost previous slide, there are other exposures to dyes. For example, in cough and pain syrups. And at a scientific symposium on dyes held last month. There was some new data presented on this, which indicated that children can be exposed to pretty high levels of dyes in these kinds of syrups.

So I'd like to just focus on what is the evidence that has not, that was not considered by FDA in 2011. So as your background materials show there two additional meta-analyses. There've been six additional major scientific reviews of the evidence and then a number of other reviews or studies that I would say provide additional support and evidence on the growing consensus around dies and behavior. Also four animal studies that reported no observed adverse effect levels that were lower than those used by FDA to establish its ADIs, meaning that those ADIs are likely too high.

Okay. So the next three slides discuss some of the major reviews of diet and dyes and behavior. And I've highlighted the ones that were not considered in 2011. So in 1983, there was a major review, a meta-analysis that did not find any effect between a diet that eliminated dyes and some other substances and hyperactive behavior. And after that 1983 meta-analysis, it was believed for the next 20 years that a food dyes did not have any adverse effect on behavior.

There was another study in 1997 that did say

that there was a role, but really the Kavale and Forness meta-analysis pretty much shaped the thinking that began to change in 2004 with a small meta-analysis published that found that when you excluded the smallest and lowest quality trials, a small effect size about 0.2. You have in your background material, the Nigg meta-analysis, it found about a 0.27 effect size when looking at objective tests of attention.

Okay. I'm trying to advance. Okay.

So there've been a number of other reviews, some qualitative some quantitative. I'll talk a little bit more about the Sonuga-Barke. But again it's showing an effect size of about 0.42, a little higher. We'll discuss why. And there've been some other reviews. The ones by Arnold in 2013 and Faraone in 2014, used evidence-based medicine criteria to evaluate the strength of the evidence. And all of these are finding that yes, there is a small effect with elimination of dyes.

And then this one in 2014, also by Nigg, did both a qualitative and quantitative analysis. And the conclusion was that a small, but extensively discussed

literature yields and emerging consensus that dietary intervention to remove additives, color, and perhaps preservatives likely yields a small aggregate benefit.

And I'd really urge the Board and FDA to consider inviting Dr. Nigg to make a presentation because I know that he has continued to analyze this data and update it.

So I just want to speak a little bit about the 2012 meta-analysis. As you know meta-analysis is the state of the art method for synthesizing all available data. And it's particularly useful in this context where we have many small randomized controlled trials.

So I know this is a little bit crowded, but this presents his 2012 results. And on the left there you see all of the studies listed. Those are double blind, randomized controlled trials, which is of course the gold standard for establishing causality. And at the bottom you'll see that there's a scale that goes from minus 0.5 to plus one. And those are the effect sizes. An effect size of zero means there's no effect meaning no dyes, dyes. There's no difference.

Results to the right of zero indicates that dyes, food dyes are making kids worse to the left. Food dyes are making kids better. And the diamonds, which I've circled in red are the pooled results. And the width of the diamond shows the confidence interval.

So what you can see is for the top and the bottom diamond, they do not touch zero. They're there. In other words, we can be fairly certain that there really is an effect here. The middle diamond just touches zero, so it's results are short a statistical significance. What you can see though is that these are pretty consistent results in terms of effect size, not a huge effect, but an effect.

So these kinds of effect sizes are not hugely significant from an individual standpoint, but they are important at a population level, especially when a large number of people are affected. And I also just want to draw your attention to last diamond there on the attention tests.

So this is the first meta-analysis to look at objective tests of attention, which is very

important because those are not subject to problems with blinding or the raters beliefs. So that's very significant.

And this shows the results for restriction diets. Again, the diamond shows the pooled results are outside, you know, we have, we have confidence in these results that there is a small effect size.

And this is the Sonuga-Barke 2013 results. The red boxes are the effect sizes. The bars are the confidence intervals and the blue boxes show the pooled effects. If you look at the chart on the right, that's artificial food color exclusion and you'll see that the blue box does not touch -- the confidence interval does not touch zero. For the restricted elimination diets, it just fell short of statistical significance.

So this meta-analysis is different from the last one because it was restricted to children that had a formal diagnosis with ADHD and it came up with a slightly higher effect size probably for that reason. It also looked at studies that were, you know, the best -- probably blinded. So again trying to deal

with the issue of problems in blinding in some of the studies.

I'm going to very quickly run through other some of the other qualitative reviews, but I don't have time.

So this used the Oxford Center for Evidence-based Medicine criteria to evaluate the strength of the evidence. FDA approved medications got a five, artificial food color exclusions got a four. Much higher than other nonpharmacological treatments such as psychotherapy, which got a one.

Okay, I'm waiting. Sorry. Technical problems here. Okay.

And I don't have time to go through all of these, but FDA was aware of this 2010 study, but it indicated on its bibliography that it did not review it, but it's actually very important because it provides some important mechanistic evidence that may explain why some children react to dyes and some do not. And it has to do with polymorphisms in a histamine degradation gene.

So in terms of any research going forward,

it would be very, very interesting to screen children that have this polymorphism from those that don't, that may explain why some children seem to react and some children don't.

And then there are these other reviews that I don't have time to discuss at the moment. But I do want to just briefly pause on the Lok study in 2013. When they removed food dyes and other additives from the diet, they found that that reduced the level of problematic behavior. But when they challenged the children again, they did not find an effect. Now they did not use the same dye mixture that was used in the Southampton study. And they also used a different form. They used a pill rather than a beverage. So it's not at all a replication of the Southampton study. In fact, the Southampton study was a replication of the Isle of White study and it confirmed the results in three year old children.

So yeah, this study did not use what we would call Red 40 and it also had additional exclusion compared to the Southampton study.

The Pelsser review acknowledged that the

effect size of artificial food color-free diets was in the small to medium area. And then here are some of the other reviews, but they're all basically supportive of this link. As you can see here. This was one that looked at EEG effects -- sorry, waiting.

And again, I mentioned that these report no observed adverse effect levels that are lower than that used by FDA in establishing its ADI. If you added up FDA's ADIs and compared that to the dose that triggered reactions in an FDA-funded study from 1982 by Weiss, et al. you'll see that those that adds up to be over 15 times the amount triggering reactions in FDA funded study. Many other studies used lower doses than that and found effects.

So it doesn't take much for a child to consume, to trigger adverse behavior that was observed in these clinical trials. I also just want to bring the Board's attention to an assessment being done right now by the California Office of Environmental Health Hazard Assessment. This is approximately a year long effort where they're evaluating the toxicology, epidemiology, clinical, and exposure

literature and databases. They've done a data call, which has now ended, they held a scientific symposium last month where there was some new information presented and there'll be a scientific peer review and public review period of their report. And this is obviously going to be very relevant to the question before the Board and the agency.

So in conclusion, dyes contribution to ADHD and behavioral problems is real, although modest and entirely preventable. And I assumed that the Board has received the sign-on letter signed by six organizations and 14 scientists affirming this conclusion. This is not just my conclusion. And the California OEHHA assessment will provide additional information. Some children are markedly affected, others are unaffected, and we have some genetic information about why that may be. And banning dyes or providing information on the label that dyes may affect behavior is really the only public health approach that we know of for reducing hyperactivity and related behavioral problems.

Thank you.

CHAIRMAN MCLELLAN: Thank you Ms. Lefferts, we appreciate the Center for Science and Public Interest and the report.

Committee I should explain when you call for public opinion, it's everything from personal conjecture, opinion all way through to detailed work. We do not, you know, query that it's as a standard practice. So just, just to explain Connie.

So anyways so we're going to move on and now move into our FDA board assessment and discussion with our experts and we're fortunate to have Susan Mayne, our Director for Center for Food Safety and Applied Nutrition with us. And Susan, maybe you can help with the introduction of your entire team here if you would. I appreciate that.

DR. MAYNE: Great, thank you. I think you heard earlier in the opening remarks about the importance of science that underlies everything we do.

We are a science-based regulatory public health agency and so we do appreciate getting your input on some of the scientific issues that we are challenged with here today. Just a comment from the

perspective of CFSAN, is we do have a large number of scientists working within CFSAN. It's really important to our mission in so many ways.

We have a big contingent of chemists and microbiologists and toxicologists. We also have nutritional experts, epidemiologists, biostatisticians, and consumer studies experts. And in that lies is the foundation of so much of what we do. So we seek all of that multidisciplinary input in the work that we do within CFSAN.

And part of the reason that we have a, you know, such a large contingent of scientists within the agency is because so much of the work we do in the food and nutrition spaces in post-market and that is we have to be prepared to respond to things as they arise and things arise quite frequently. So I just wanted to emphasize our commitments to science, obviously, which is really important to the Science Board. And the strong foundation that we rely upon within our science.

So our policy is always based upon sound science and we really are looking forward to getting

your input on today's topic on color additives and behavioral effects in children. And I think I'm going to move it over next to a Dr. Dennis Keefe, who is the director of CFSAN's Office of Food Additive Safety and he'll introduce his team that's going to be making the presentation today.

So Dr. Keefe.

DR. KEEFE: Well, thank you Susan and thank you to the Board for taking this topic on. My name is Dennis Keefe. I'm the Director of the Office of Food Additive Safety. This office is responsible for the pre-market review of food additives, color additives, grass substances, new varieties of plants.

This issue of the relationship between color additives and food ingredients as mentioned by previous speakers really arose first in the 1970s with Dr. Feingold, when he put first put forward his proposal of the link. This has been looked at several times by NIH, by FDA. You've seen some reports of EFSA and also JECFA looking at the relationship and also the safety of these color additives.

Today, we want to revisit this topic with

the Science Board to get your take on the views of the current science. So with that in mind I brought some of my team with me today. Dr. Andy Zajac. I've got Scott Thurmond, who is a toxicologist from the office who will be presenting giving you an overview. And behind me is Dr. Diana Doell, who is a chemist in the Office who has been involved with the exposure assessments for the color additives.

So with that in mind Dr. Thurmond is going to give you a brief overview of the history of this issue and sort of where we are now with the science and to get your views. So again, I want to thank you for your participation in our discussion of the science of the relationship between colors and hyperactivity. So with that, Scott.

DR. THURMOND: Thank you, Dr. Keefe.

Well, let me go back. What I want to do is basically give you a quick background on the issue. It won't be in-depth by any means. Then I'm going to talk about the 2011 Food Advisory Committee that the FDA brought together to evaluate the food FD&C color additives and ADHD issue in children.

After that, I'll talk a little bit about the exposure assessment that we just -- back -- was concluded in 2016 and published during that period.

After that, I'll update the literature little bit about what we've looked at since then and after that there'll be the questions to the Board.

So anyway, the brief history has been mentioned in the 1970s, Dr. Benjamin Feingold proposed that certain additives such as an artificial food, colors and flavors, preservatives and natural salicylates can trigger allergic-type reactions and behavioral changes in children. He based this on his clinical observations and he presented this information at the annual meeting of the American Medical Association.

Based on this his findings, he devised an elimination diet, which is often called the Kaiser Permanente Diet, and he eliminated the artificial food colors and flavors and preservatives such as butylated hydroxytoluene and butylated hydroxyanisole, as well as foods containing natural salicylate, which is a large number of fruits and some vegetables. Also,

coffee is in that.

So he, in using this elimination diet in his practice, he claimed there was a 60 to 80 percent success rate in the lowering the hyperactivity of the children that received this diet. Based on this work by Dr. Feingold, the entire field of stimulated -- it was stimulated, the field of research examining the possible dietary triggers of problem behaviors in susceptible children.

In 1982, the NIH empaneled a Consensus Development Panel to evaluate the data on defined diets and hyperactivity. And they concluded that the limited, there was limited positive association between defined diets and decrease in hyperactivity. They also noted that the decreases in hyperactivity were not observed consistently. They identified some data gaps including a lack of standardized diagnostic criteria, a role of predisposing factors such as genetic, developmental, and environmental, and the lack of longitudinal perspective studies.

They finally concluded that this defined dying approach should not be universally used in

treatment of childhood hyperactivity.

In 1986 the FDA formed an advisory committee on hypersensitivity to food constituents. They evaluated the available data to adverse reactions associated with food ingredients, including FD&C Yellow No. 5. And they did not find any evidence of behavioral disorders associated with the food ingredients evaluated.

That brings us to 2007 and the Southampton study, which was published in Lancet in that year. The study itself was commissioned by the UK Food Standards Agency. It was a six week study to investigate whether certain mixtures of color additives and a preservative, sodium benzoate, which was used cause adverse behavioral effects in children from the general population; three years old and eight to nine years old.

There were two mixtures used in this study. One was Sunset Yellow, which we refer to as Yellow No. 6. One was carmoisine, which is not allowed for use in foods in this country and tartrazine which is analogous to Yellow No. 5. Ponceau 4R, also not

allowed for use in this country infoods and sodium benzoate. Mix B was Sunset Yellow, carmoisine, Quinloline Yellow, not allowed for use in the US, Allura red or Red 40 and sodium benzoate.

In their paper, they reported adverse effects on behavior of three year old children with Mix A, but not Mix B. And adverse effects in eight to nine year old children with both Mix A and Mix B.

It should be noted that it's unclear whether the Sunset Yellow or the others with analogous FD&C codes underwent batch analysis, which we FDA requires for any FD&C color to ensure their purity and composition.

So, you know, and the other thing is that for all FD&C colors that are used in products they're required to be labeled on that product. In other words, they have to state what the FD&C color is and that goes for all the FD&C colors.

So in 2008, EFSA completed the assessment of the Southampton study. They concluded in their review that it provided only limited evidence that additives had a small effect on activity and attention in

children. They also weren't quite sure what the significant of the effects were. They were a little unclear. They finally decided that the study cannot be used as a basis for altering the acceptable daily intakes for these colors or the ADIs.

In 2009, they did a more thorough scientific evidence search and then concluded that they did not disagree with the previous decision of the 2008 panel. And that the evidence does not substantiate link between color additives and behavioral effects.

So in 2011, the FDA brought in our Food Advisory Committee to evaluate the data that had gone on before and make the decision, you know, to help us get a better idea of what the issues, if there were any issues related to FD&C colors, either behavioral or in ADHD. The charge to the Food Advisory Committee was to consider the available relevant data on the possible association between children's consumption of FD&C color additives in food and adverse behavioral effects. We also asked the committee to advise us on what action, if any, is warranted to ensure the safety of these color additives.

At that meeting the FDA presented its review of 33 clinical trials including the Southampton study that were relevant to the association between artificial colors and ADHD and related problem behaviors.

These were the criteria that our expert reviewer looked at in these studies. All the studies did not have all of these criteria and it was up to the reviewer to determine which ones, whether or not the ones that were missing were critical to interpretation of the findings from those studies. There were 10 criteria there. So after our review of the 33 studies, the FDA concluded that a causal relationship between exposure to color additives and hyperactivity in children in the general population has not been established. And we also noted that there is no definitive evidence of a biological mechanism for effects on behavior.

However, as Ms. Lefferts has noted, the data suggests that for certain susceptible children with ADHD and other problem behaviors their condition may be exacerbated by exposure to a number of food

substances, including, but not limited to artificial food colors due to a unique intolerance and not to any neurotoxic properties.

The Food Advisory Committee, you know, in their conclusions after listening to all the input they decided that the causal link between children's consumption of FD&C color additives and adverse behaviors are not established by the available data. This did not contradict the FDA's findings on that. Additional label information such as a warning labels, as they do in Europe were unnecessary to ensure the safe use of the FD&C color additives.

In response to our question about additional what we need to do additionally we did -- they recommended that further research which was needed, including additional safety studies. Well, the FDA looked at the literature and decided that the animal was not a good model for assessing hyperactivity in humans or intolerance to certain compounds. So we have not addressed that particular recommendation.

They also wanted us to do a comprehensive exposure assessment for these compounds. In the next

couple of slides, I'll talk about that exposure assessment that was done.

Here is the study or the structures of the compounds -- of color compounds that we evaluated in our exposure assessment. Notice that say Red 40, which is known as Allura Red in Europe. And the Yellow 6 and Yellow 5 are also, you know, included in that batch. Not only do these -- are these structures different for many of the colors, but they're also in different chemical classes.

So the exposure assessment for FD&C colors for the US population was based on data that our FDA chemists developed or that was -- excuse me -- we had, you know, analyzed from -- was it 2012 through 2014. We did analytical data on 600 representative foods sampled in that -- during that collection period.

The dietary exposure for each color additive was estimated for a population two plus years of age and for children two to five years of age and teenage boys, 13 to 18 years old. You may wonder why we looked at teenage boys in that. Well, it turns out teenage boys are the biggest consumers of products

containing these FD&C colors.

So anyway, the study was published in 2016 in Food Additives and Contaminants Part A to Peer Review Journal. And the final outcome from the exposure assessment was that the estimated daily intakes were well-below the acceptable daily -- accessible daily intake levels. In other words, the ADI levels.

Okay. We did a little updated literature. We don't have all the studies that were pointed out, but these are the critical ones that we felt needed to be evaluated. The Nigg, et al. 2012 study has been, you know, mentioned before and these meta-analyses, it was basically a meta-analysis study on the role of diet and food colors in ADHD. The Sonuga-Barke study done in 2013, was a meta-analysis study on dietary and psychological interventions as treatment for ADHD. And the Lok, et al. study in 2013 was a double blind placebo controlled clinical study in children using color additive mixtures. The Pelsser study in 2017 was a systematic review of several meta-analyses of clinical studies on various dietary factors including

color additives and their possible role in ADHD.

The FDA's conclusions on the Nigg, Sonuga-Barke, and Lok studies was that there were no reliable challenge effects were found in the Nigg study, there were no reliable challenge effects were found with parents and teacher/ observer outcome measures when the analysis was restricted to the FDA approved colors.

In that study, they allowed for the publication bias. They removed publication bias from that, which basically showed that very few of the colors that were used had any impact on ADHD in these children, the Sonuga-Barke, et al. paper. They had -- findings and our reviewer -- our findings did not support the use of artificial food color exclusions as an efficacious dietary intervention in the nonpharmacological treatment of children with ADHD and related problem behaviors. The Lok, et al. study, which was done in Hong Kong, Chinese children at the age of eight to nine years of age. We determined in our review that the study did not show any significant adverse effects from either the mix of four artificial

color additives or the sodium benzoate preservatives on the behavior of the Chinese children in that age range.

Okay. The Pelsser, study we've just found that. We did a literature search in early or mid-2019, which is why we may not have picked up the study that Mr. Cox noted in his presentation. But the Pelsser study was published in Plos One in 2017 and the article title was “Diet and ADHC: Reviewing the evidence, the systematic review of meta-analysis of double blind placebo controlled trials evaluating the efficacy of diet interventions on the behavior of children with ADHD.”

Basically, their method was they did a search of the literature and found six meta-analysis that matched their criteria of double blinded placebo controlled trials that applied homogeneous diet interventions. They determined an effect size and confidence intervals for each dietary intervention and the authors concluded that the effect size of artificial food color-free diets was small to medium such that the dietary intervention that excludes AFC,

should not be advised as a general ADHD treatment.

Okay. Now we come to the questions to the Board. We have had three questions that we've looked at and gone back and forth on. And the first one is, does the latest science establish a link between consumption of FD&C color additives in food by children from the general population and adverse effects on their behavior. Second is, does the latest science establish at the use of artificial food color exclusion diets as an efficacious intervention in the nonpharmacological treatment of children with ADHD and related behaviors. The third is, since the 2011 Food Advisory Committee, are there any new consideration in terms of design characteristics of a study intended to test the hypothesis that there is a causative link between the individual color additives and ADHD in children? Have there been any new tools developed since 2011 that may be considered to be used in the conduct of such a study.

And thank you for your attention.

CHAIRMAN MCLELLAN: Thank you Scott. Appreciate that. And I think that's the end of the

oral presentations here.

So Board, we, we also have joining us on the phone to two additional experts beyond those introduced here. But I think Sherry Ferguson and John Chelonis is here. Is -- are they on the phone?

DR. CHELONIS: Yes, John is here.

CHAIRMAN MCLELLAN: Thank you John.

DR. FERGUSON: I'm here, too. Sherry Ferguson.

CHAIRMAN MCLELLAN: Thank you Sherry. Could you all introduce yourself in terms of your background, just so that we understand who you are as experts on behalf of FDA?

DR. FERGUSON: Well this is Sherry Ferguson and I am Division Director of Neurotoxicology at the National Center for Toxicological Research. I've been doing work in Developmental Neurotoxicology for almost 30 years now. I'm not sure I would consider myself an expert on color additives and their effects, but that gives you just a bit of history.

DR. CHELONIS: And I'm John Chelonis. I'm with the National Center for Toxicological Research,

as well. I've been doing behavioral work with children for about 20 years now and we have done some work on looking at the effects of methylphenidate on children with ADHD. Once again, I'm not an expert on color additives, but I have done some work assessing children with ADHD and looking at stimulant medication.

CHAIRMAN MCLELLAN: Very good, thank you both. I appreciate that.

So Board members at this time we, we would welcome you to comment, to ask questions of our FDA experts both here and on the, on the phone.

I am interested in seeking your opinions here and so I would ask you to draw opinions. Okay. That's a value to us. And at this point I think what I would like to do is tackle each of these questions one at a time. Unless you feel there's an automatic tie across the three, then, then feel free tto explain that and we'll go from there.

I'm not going to -- we're going to leave the questions up so everyone has those in front of you and we can proceed from there.

So Rich, I think you were the first one up. So I'd ask you to go ahead. Thank you.

DR. LINTON: I have a question but I'm not exactly sure how to address it or who to address it to. But the question is related to the California study that is beginning. I'd like to have a little bit more information about the charge of that group. The timeline for the work to be done and also how the project is being funded.

DR. DOELL: Hi, I'm Diana Doell with the Division of Food Ingredients in the Office of Food Additive Safety. That group -- it was resulted from a Senator from California, that charged the California EPA with looking at the, looking at color additives in any neurodevelopmental effects on children. And we met last month and there were a lot of experts there, toxicologists, pediatricians, the government and industry and they're going to take all of the information there and continue that study and they are supposed to have a peer reviewed report out next summer.

CHAIRMAN MCLELLAN: Barb.

DR. KOWALCYK: I'm Barb Kowalcyk. I had a couple of questions. One was in the first question is "established a link," do you mean a causal link or an associational link?

DR. THURMOND: We've been trying to establish a causal link.

DR. KOWALCYK: Okay. Well, it wasn't clear from the question.

DR. THURMOND: Sorry.

DR. KOWALCYK: So the the second question I had was, I believe it was Dr. Cox had mentioned a more recent meta-analysis by Cagigal, et al. and from 2019. I did a quick search online and could not find a copy of that meta-analysis. Have you looked at it?

DR. THURMOND: No.

DR. KOWALCYK: No. Okay. And then my final question is CSPI gave a definition of safe and I wanted to know if that was the definition or the level of evidence needed to determine by CFSAN, if a colored additive is safe.

DR. KEEFE: So this is Dennis Keefe. The safety standard that's embedded in the statute for

color additives and also for food additives is a reasonable certainty of no harm under the intended conditions of use.

DR. SARWAL: Hi, this is Minnie. Can I ask a quick question on the phone?

CHAIRMAN MCLELLAN: Sure Minnie. This is Mark.

DR. SARWAL: Yes, thank you so much. Thank you for all those presentations. They were very enlightening and a really well presented. I had a question as we're looking at causal associations. Are we able to from this meta-analysis be able to stratify the impact of this effect as it stratified by age? So like is a really younger age group perhaps more susceptible than the older because childhood is a broad age range and also is there variations by gender and in addition also, is it a variation by if the child was premature and therefore maybe more susceptible? Do we have that kind of information?

Sorry, that is my question.

CHAIRMAN MCLELLAN: What would you like her to restate that or --

DR. SARWAL: Was it not clear?

DR. THURMOND: Yeah, restate that. I'm not sure we have an answer for you, but please restate that.

DR. SARWAL: Yeah, I was just wondering, because you're looking for causal associations. Are there inherently more susceptible populations within the child category? You know, the broad category of childhood, the age range, and so is there perhaps has the casual association being stratified to take into account the very young aged recipient children, who may actually have been very premature and therefore more susceptible, their brains may be more susceptible. And the other thing is by gender. Is that risk stratification possible with the data as it exists today?

DR. THURMOND: That's a tough question to answer. I think I'm going to ask Dr. Chelonis to weigh in on that.

DR. CHELONIS: Well, as I said before, I'm no expert on the color additives but just looking at these meta analysis you guys provided. It seems to

me, you know, the populations and everything all across the Board. So I don't think we have enough studies really to be able to even think about stratifying anything at the moment.

DR. STEELE: Yeah. I mean that the outcome measures aren't even the same across the studies. Right?

DR. CHELONIS: Yeah. I mean, some are looking at behavior, some are looking at parent ratings, some are looking at teacher ratings, you know, as a bunch of different things. If you look at the Sonuga-Barke article.

So, you know, I'm not, I think your question is a very good one I think are things, you know, that definitely, you know, there's some small, small suggestion perhaps, but you know, it's nowhere near as significant. There might be some cases where, you know, you might want to look at these food additives in more detail because, you know, you might be able to get a specific population, but right now it's just too early to tell I think.

DR. SARWAL: Yeah. No, thank you. I think

this is really to trigger us to think, because one of the questions are these trials sufficient or do we need to be looking and generating more data? So maybe this can be something we can think about if we are wanting to design further studies.

DR. CHELONIS: I mean, one thing I was looking at with the Nigg article was you know, when you look at clinical issues, you're looking for two things. You're looking for consistent differences across many subjects or you're looking for large magnitude effects. And if you run chi-squared, looking at some of these studies that are FDA colors, you don't really see significant evidence for either one of them at this time.

CHAIRMAN MCLELLAN: Thank you. We're going to go with Ted and then up here to Sean and then Cynthia. Ted.

DR. REISS: Thank you, Mark. So I just wanted to go back into the toxicology realm for a second if possible. I know you said there's no animal models of ADHD. It's a syndrome anyway. Probably very difficult actually to model. But I was wondering

if there were any new hypotheses about what a food additive, how a food additive might affect ADHD. We talked about allergy. Do these drugs get into the CNS? Do the metabolites get into the CNS? Do we know anything about that that would lead, you know, that would help us to sort of understand whether a causal relationship or a hypothesis is present?

DR. THURMOND: Well, Ms. Lefferts mentioned the histamine possible involvement. We have not been able to confirm that or we have not seen another study addressing that particular hypothesis.

DR. REISS: Okay. Do these two, these compounds get into the CNS at all or there metabolites?

DR. THURMOND: Most of them are large molecules and they, you know, they're usually excreted in feces or very few of them get into the systematic circulation. And I'm not aware of any that even cross the blood brain barrier.

CHAIRMAN MCLELLAN: Sean.

DR. XIE: That was a very comprehensive -- I really like it. They bring up a lot of key points.

If allow me to follow the third question about -- actually this is when you ask for any model or something available -- to available.

There is approach that we use called a Bayesian causal network. It was originally developed. Then we also -- one of the developer is Greg Cooper is a biostatistician. So we use it that for other purpose. If the data is available, we can try that. But I'm not sure. This causal link is the from statistics result and analysis or is from the machine learning -- statistic analysis come up.

DR. THURMOND: I'm sorry, what was the question?

DR. XIE: Well, the definition there's no causative link. Is that the predicting from the data? Because there's a standard, there's a method called the Bayesian causal network, is a more powerful based on machine learning. We use that one, too. To identify each of the attributes.

DR. THURMOND: Okay, we may have to look into that.

DR. XIE: And then back to the second is, I

was reading an article yesterday and also in your presentation, you also show the data published in 2007 and shows -- I find that this article published by the same author McCann and publishing -- is more high impact journal 2007. And the data, they analyzing is big, 300.

And in the report you presented in 2011, so it shows that 41 children was it selected for data analysis. My point is that the sample size I like the -- although this is smaller sample size, but the people who participate in this for scoring is a parent, teacher, and also the psychiatrist is more professional, comparable with the adolescent. I mean, under the paper published in 2007, it was only parents and teacher, so I'm not sure they scoring which may effect outcome. Right?

DR. THURMOND: Yes.

DR. XIE: So you, if you can comment on those.

DR. THURMOND: In the Southampton study the authors relied more heavily on the parental feedback then for either -- they had a teacher and classroom

observers and they opted for the parental, you know, feedback to use in their analysis for the most part that -- parental -- relying on the parental observations is very subjective. I mean, if you've got a, you know, a child with ADHD and he knows he's in a study, he or she is in a study, the behavior may change just because the parent is monitoring them, is entering -- they have a little diary they're entering their activities in. So that's tough to look at that.

In our thinking that teachers and classroom observers probably, well, primarily teachers have a better feel for whether a child is, his activity is changing, whether or not, you know, they're responding to treatment. And you know, if there's nothing there, if they can't report any change, you know, that's a problem for the you know, for the people who are running the study.

DR. CHELONIS: Yes, this is John Chelonis. If I can chime in for a second, I mean, one of the criteria for ADHD is to have you know, problems across two settings. I mean, part of the reason for that is to make sure it's not, you know, just the parent

interacting with the child or the teacher interacting with the child. That's problematic. So I would give a lot more weight to studies that are looking at both parents and teacher reports then to studies that are just looking at parent reports solely.

CHAIRMAN MCLELLAN: Okay, good. I've got Cynthia, Barb, Ted again? No. Okay. And then Dojin. So Cynthia, please.

DR. AFSHARI: Yes, thank you. You know, what struck me, listening to the multiple presentations this morning were two things. I think. One is that I'm certainly thinking about the epidemiology and you know, that isn't my area of expertise, but I know we have others. You know, it just seems that all of the studies are confounded with multiple variables and we haven't heard much discussion about that. In terms of what else is confounding in these subjects and how might that influence and you know, we're focusing on a specific aspect here, but I think providing that balanced view and analysis is important.

I think the second one was where Dr. Reiss

was going, which was just on the basics of the toxicology and it may be worthwhile to revisit that in a more formal, systematic manner. I know it was brought up around the NOAEL and whether there's evidence or not to suggest that the NOAEL is different from how it was previously described, you know, and whether that is the basis for setting the ADI.

I think that we heard that, you know, maybe diets are shifting or maybe there may be certain people who have more exposure, but I think again, in that classic kind of PK tox relationship to just show how much of a range of safety margins or multiples do we have above kind of were adverse effects were determined or the ADI levels around different individuals.

And I certainly think that piece that came out around the fact that the compounds are large, they're excluded from the CNS. You know, again, if there aren't any individual variants that suggest altered metabolism, I mean, all those points which are classic kind of PK tox models are I think are very relevant and could help provide, you know, either

points to sensitive patients or actually alleviate some of the concern from a human exposure perspective.

CHAIRMAN MCLELLAN: Thank you. Barb.

Sorry, if you wanted to comment you're welcome to.

DR. THURMOND: All right, all right. I wasn't sure whether you were asking for a comment or making a statement. Yes. Those are issues that, you know, the, the multivariate issues related to ADHD colors. That was the 1982 NIH study pointed that out. Environmental, you know, the genetic components. I mean, these are things that are difficult to take in any, the human studies looking at this type of interaction, dietary colors or whatever are extremely difficult to do and do them reliably.

You know, there were, as I noted, there were 10 criteria that our expert reviewer was looking at in terms of, you know, the studies that we had reviewed. And you know, it's difficult to find studies that have all the components you would like to have.

DR. KEEFE: I wonder also, I wonder also maybe Diana Doell, Dr. Doell can comment on the margin

of exposure issue you raise in terms of the ADIs that have been established versus our more recent exposure assessment for these colors?

DR. DOELL: Yeah, for all of the color additives that we looked at in our exposure assessment, we are about an order of magnitude below the established ADIs. So we definitely had a large -- a lot of leeway in there between the consumption of each color additive and the ADIs.

CHAIRMAN MCLELLAN: Very good. Barb.

DR. KOWALCYK: So I had a couple of follow-up questions. One I think Ted had asked you about studies that looked at the models the toxicological models. And you said you haven't seen another study. And my question was, does that mean that no one's looked at it or that, you know, people have looked at it and you haven't seen that evidence?

I mean, as a statistician, okay. I go back to the old adage is absence of evidence is not evidence of absence. And as I was reading through the packet, that's kind of what struck me. And so, I wanted to find out if just clarify is that because no

other studies have been conducted or they've been conducted and they haven't been -- and they haven't found a link.

The other question I had is I noticed in going through the meta-analyses, but most of these studies are very old and a I was just wondering if you had done in, and I think somebody had mentioned or I read it, that they hadn't looked at publication bias in the sense of -- had people been looking at, have people looked at this since the 1970s, 1980s and found no evidence so therefore they're not publishing or is it that this research just hasn't been taken up in a whole lot of detail since then.

Because if you look at the studies that are included in those meta-analyses, most of them are from the seventies and eighties. And so, the question that arose to my mind is it a function of people aren't studying it or people are studying it and that there's nothing there. And I don't know what the answer to that, but I was wondering if the agency had looked into that as a possibility.

DR. THURMOND: That's a very good question.

And no we haven't. It's something that ,you know, we involved our biostatisticians at some levels, you know, for a review. But I think we need to plug the biostatisticians into more recent findings and take a look at the data from a biostatistic standpoint. We're open to any suggestions. This is just the part, you know, this is why we were asking the Board, you know, to appear before the Board. We need any other feedback that you can give us and that's good feedback.

DR. KOWALCYK: So I know it's a very difficult to try and figure out is how these studies been conducted, but not published. But one thing that just occurred to me is, I mean, have you reached out to your colleagues at NIH and seen if people have been submitting applications for studies that, you know, which will give you a sense of, is this even on the radar of or reached out to the community that's engaged in this kind of issue to see what kind of research is being conducted?

DR. THURMOND: That's a good question. Thank you for asking it. If you've ever looked at

ClinicalTrials.gov and then did search on ADHD through there, there are over 1,200 studies that are either completed, planned, recruiting or whatever on every possible modality, you know, naturopathic treatment, dietary supplement treatment, drug, multi-drug, psychological treatment.

There's only one study out there that I'm aware of that specifically looks at artificial food colors and ADHD and that study was supposed to have been completed in August of last year, but according to the website, they're still recruiting people for it. So it's a difficult topic. You know, how do you design this study to get all the variables that you may or may not consider to be important and that's it. We don't know what variables may be that important in assessing ADHD and dietary restriction diets or whatever. You know, and so it's -- I don't know, it's a tough, tough nut to crack as they say.

CHAIRMAN MCLELLAN: Thank you. Dojin.

DR. RYU: I'm mostly trying to link this with mechanistic studies. So if you go back the original study suggested the allergic type reactions

versus behavioral changes. I tried to look it up but have not successful in digging more evidences or studies even involving or linking allergy reactions versus behavioral changes. Have you seen any other studies or results or any suggestions?

DR. THURMOND: I think there was that one study that -- let me see. Yeah, the Sonuga-Barke conducted where they were looking at psychological as well as dietary elimination types of approaches and psychological.

I'm not familiar with anything. Maybe somebody else, Ms. Lefferts or you know, Mr. Cox is familiar with that.

DR. RYU: So maybe my ultimate question is where do we can eliminate immunological reaction from the possible factor in triggering behavioral changes or not?

DR. THURMOND: That's a good question. Can we eliminate it? I don't know. I feel like I'm, you know, I feel like I don't have the answers you're looking for, but we don't have the answers we've been looking for.

CHAIRMAN MCLELLAN: Thank you Dojin. So we're going to go on to Connie and then Ted.

DR. WEAVER: I was wondering if we could spend a couple of minutes sort of on context and practical implications like from your exposure study, do you verify what we read in one of our background materials by Holton, in a the 2016 review, he said the major sources of color additives are medicines, vitamins and fruit juices. What about desserts and candies and other things? Where is the exposure?

And then where there's the exposure, what's the need for them? Is it only a marketing competitive issue or are there new categories of foods with nutrients to encourage that children wouldn't consume and therefore may be at risk for getting some of the nutrients that go along with those foods because they wanted a certain color or whatever.

And then if there were alternatives, like a lot of the reviews suggest why isn't it just prudent to take them out? But if there's a need to get children to eat those foods, then the alternatives, the natural sources that aren't synthetic, are they

safer? Do we know that?

DR. DOELL: There were a lot of questions -- so I'm going to try to address all of them. From our exposure assessment, the FD&C color additives can be used in food, drugs, and cosmetics. And in our exposure assessment, we focused on just the foods and we looked at over 7,300 food products in the grocery store. We basically did a systematic up and down the aisles and lumped them into categories where we found these color additives. And we identified about 52 food categories that contained FD&C color additives.

Now, within those categories, not all products contained the color additives, you would have variability from some products would contain a FD&C color additive, but maybe another product wouldn't. Like macaroni and cheese. Some brands contain Yellow 5, Yellow 6, others had gone to annatto or turmeric in their formulations. And so, it just really is a kind of a formulation based whether they had the FD&C color additive.

And in our exposure assessment, we actually broke the exposure down by food category and we

identified those food categories for each color additive that contributed the most to exposure.

Some of the common categories that we were seeing were beverages, juice drinks, sometimes candy. We would see -- it would kind of would vary by category like for, I know, Red No. 3, like a lot of the decorations, the icings on cakes. So we definitely have an idea by color, which color additives are contributing the most to exposure.

Now as far as nutritional value, a lot of it is consumer preference for those products. Whether the synthetic colors, you can use a small amount of that color additive and get a quite vibrant color. With a natural color a lot of times you have to use more of that color additive and you still can't achieve quite the same coloring effect that you would with this synthetic color additives.

We have one brand of cereal that when they removed the synthetic color additive, nobody bought it anymore. Because that was the draw for that product was those vibrant colors in the cereal.

Did I get all the questions?

DR. WEAVER: No. The last one, because the natural substitutes, are they necessarily safer or have been tested?

DR. THURMOND: No. No. No concerns. We get natural colors in, in forms of petitions. And one of the biggest concerns we have is, are we looking at an allergenicity issue? Are there allergenicity issues?

The same standard of safety applies to natural as it does to the artificial. A lot of people say, because it's natural, it's got to be good for you, but you can get -- we have what we call CAERS database, which is a public reporting database that allows people to, you know, submit issues that they've had with certain food ingredients or types of foods. A lot of it's subjective. We don't have a lot of physician submitted data, but there have been some input on the so-called the natural colors, such as annatto, you know, they've had supposedly adverse effects. Whether or not it's related to annatto or some other issue, we can't determine. But for natural, natural is not any safer or less say than

FD&C colors.

DR. DOELL: And I also like to point out that in order for it to be labeled as an FD&C color additive, it does have to go through batch certification. Each batch that is produced for identity impurity before it can be used in food products.

CHAIRMAN MCLELLAN: Okay. Well, go down to Ted.

DR. REISS: So I have sort of two comments or questions. The first one maybe ties together just a little bit of the comments that everyone was making here. It seems like there's no either longitudinal or cross-sectional cohort studies in ADHD to understand some of these predictor variables.

Correct me if I'm wrong, it might help to answer some of these questions about the relationship to allergy, you know, who's at high risk predictors, these sorts of things. If it exists, please let us know. But I didn't see it in any of the background materials. That was just a comment.

The question that I have also, we've also

brought up the issue of the heterogeneity of these clinical trials and the heterogeneity responses to small effect sizes and so on and so forth. In the reports of the meta-analyses, I didn't see any summary of blinding. Well, we talked about blinding about the end points and the measurements and that sort of stuff, but the blinding of actually the color additives.

How was that done and how is it maintained, especially in these older studies that are from the ‘70s and ‘80s, where maybe people didn't pay attention to those? Do you have any thoughts or information about that?

DR. THURMOND: Well, sometimes they do a placebo, they did a placebo effect and they’d run placebos. I can't tell you what the methodologies are for all these studies, but they made --

DR. REISS: No, I mean, blinding a color additive. It's easy. You can't have the same color because it's the same thing.

DR. THURMOND: I agree. And that's difficult to do.

DR. REISS: But then the capsules can’t be clear, they have to be and the colors can change, too if there’s another color behind it.

DR. THURMOND: These products are a color or they're not a color. And you know, if it's a mixture, how do you blind a mixture?

DR. REISS: It just provides a methodologic problem in doing some of these studies.

DR. THURMOND: Yeah, it is a real challenge.

CHAIRMAN MCLELLAN: Just to comment. There are ways to visually create an abstract environment. Either, you could wash the -- it depends on how this was all, whether it was controlled design set up, but you can wash a room with intense color that washes out all of this anyways. Just a comment.

Okay. I think we're coming up to Dojin next and then Connie and then Tony and then -- back to , okay -- go ahead.

DR. RYU: Part of what I want is to follow-up questions from Connie. But before that I'd like to mention that this survey was done really nicely and I cannot imagine going through all the analytical

testing of individual samples.

But about the analytical part, I assume that all the matrix effect has been you know, challenged and scrutinized to get that any recovery or the extraction errors.

DR. DOELL: Yeah. Depending on the product, it had an extraction method that was for that type of matrix. So there were things for dairy that may be different from a beverage and those were taken to account in the masking method. And then the nice thing about the method is you can analyze for all seven color additives in one run.

DR. RYU: Yeah. I looked at the original article and it was well-developed. So if you could do the exposure assessment in considering, I mean, including medicines like over-the-counter drugs, that the end results would go up to the any significant level of concern or not, you know, currently study is not at all, but if you add them up, would there be any possibility that the level could be of concern?

DR. DOELL: I think that's a hard question because food is something that you're eating daily and

it's a chronic thing, but a lot of medications, you're taking it for a short period of time and then you're no longer taking it. So you're comparing a chronic type of exposure more towards an acute type of exposure.

So it's two almost different variables there. Something we could look at is an exposure assessment with the drug products, but we would just need data on the levels of the colors in those products as well.

CHAIRMAN MCLELLAN: We're going to go onto Tony. But I'm going to comment here that I'm looking for some speakers that may be haven't engaged a little bit. If you are not finding yourself to a conclusive or explorative place, take us to a questionable place. Take us where you're not seeing stuff that you'd like to see stuff. Tony.

DR. BAHINSKI: Thanks Mark.

I have many of the same comments that many of the folks on the Board have already expressed regarding the you know, kind of the gaps in the robust study design with a lot of the clinical trials and

other studies that have been presented to the Science Board.

And maybe it's in relation to Point 3. I've been aware, just recently there's a new paradigm, you know, with certain journals called the Registered Reports and especially conducive to, you know, kind of neural behavioral studies of this sort. Where basically the editors find that there's an -- you know, the subject of the study is important. I would think something like this will qualify.

And then the peer review is done on the study design. And so, I think that would, you know, try and get around some of the issues that we've seen with, you know size of the population, you know, potential biases in the outcomes.

And then, the publication is actually accepted at that point for publication regardless of the outcome of the study. And I think that speaks to what Dr. Kowalcyk was bringing up. You know, are we not seeing studies coming out because they may be negative. And so, there's some kind of publication bias there. And I think that's the whole point of

these kind of Registered Reports.

And I think more and more journals are picking this up. I think it's relatively new concept. It's about 200 or so that are in there now.

I don't know if there's a way to encourage people in this field that, you know, to submit that because I think that's a way to get some unbiased, you know, robust study design that can help us get to some of the answers here.

DR. THURMOND: Well, I know years ago in academia that publishing negative data was not encouraged. And we've always argued that that negative data can be the most informative because you look at what they publish and you know, well, they did something wrong here or there or maybe, you know, the power of their study was not great enough. So, you know, there are a lot of issues there and I think I agree there are more and more journals that are accepting negative outcomes in terms of publications.

DR. BAHINSKI: Right, but I think it's that upfront review of the study design. It's critical there.

DR. THURMOND: Exactly.

DR. BAHINSKI: It's hard to do it on the back end. Right?

DR. KEEFE: If I could just jump in, this is Dennis. You know, the 2011 FAC also recommended certain criteria for conducting a study to address these sorts of gaps that we identified in 2011. And I think from the discussion here, I think, we still see that there are a number of gaps here in our dataset.

I wanted to come back to a point from Dr. Weaver about the colors and whether there's benefit or not to adding the colors. Under our statutory regime, the approval of color additives and food additives is based on safety only. It's not a safety benefit or you know, a marketing benefit or anything. It's purely a safety decision and whether or not at the additive -- the color additive or the food additive, you know, has a penetrance in the market is successful. That's entirely up to the market and technology. So we don't weigh in on that.

DR. ZAJAC: And also I just wanted to add that there was the question about why are color

additives added to drug products. Sometimes they are added to differentiate one drug from another drug. So you may have a blue tablet versus a purple tablet. Sometimes the color is also added so that the color is consistent with the flavor in that product as well.

CHAIRMAN MCLELLAN: Just a quick side comment regarding access to data. Of course, since 2013 the OSTP guidance for extramural funding requiring public access is changing everything in the universities. Most universities are taking that approach that it is the data must be accessible, whether it's a negative result or not, it must be available. So that may change things in the future for us. Barb, you were next.

DR. KOWALCYK: Okay. Barb Kowalcyk. I think Mark is hoping we'll start to address the questions here. So, I'll just take a stab at it.

The first question I'm not sure that we can say that there is sufficient evidence that there's a causal link between consumption of these causative additives and adverse effects on their behavior. Conversely, I don't think there's enough evidence to

show that there is reasonable certainty that there is no association. So I think it matters which way you ask the question. So I think more information is needed before you can make a decision on that.

Second question, kind of the same thing. I don't think that there's enough evidence to establish the use of color exclusion diets as efficacious intervention, but I don't think that that closes the book on this. I think more studies are needed. I think there is enough evidence to suggest that there may be something there. I don't know if that's going to stand further -- the test of further research.

I did want to make a comment on small sample sizes since that's come up a couple times, that many of these studies have small sample sizes. When you have small sample sizes you worry about underpowering a study. So if you find a significant difference in a study with small sample sizes, then I think you can have fair confidence in that. If you find no difference in a study with small sample sizes, then you have to worry about it being underpowered.

Now if your sample size is so large that you

detect differences, but they're not clinically meaningful, that's also a problem, being overpowered. But I don't think any of the studies that we're looking at here have -- I was not concerned about this study is being overpowered based on what I saw. Okay.

And then thirdly, so I just wanted to mention that because many people, including some of the reviews had commented on the small sample sizes and that really didn't concern me. Only in the fact that I would be cautious about interpreting no significant differences from those studies.

And the third question, I do agree that there are some other ways and I agree with Ted that looking at some cohort studies or cross sectional studies would be very valuable. I wonder if there are studies that are already being conducted in children with ADHD that do comprehensive dietary assessment on these children over long-term. And would it be possible to utilize that data and combine it with data on the level of these colorings in those food products to actually come up with estimates?

So that was something that I wanted to point

out that that may be able to be used.

Of course it is difficult to prove causation in those types of studies, but it might give us some valuable insight into some of the potential confounders that are present and would give you very large sample sizes which is what you need to be able to start looking at those.

And finally, I know there was a question about -- a question about how to mask color. I know that there are some -- I think some of the studies were using cookies or chocolate cookies to mask the color. Of course that brings up other potential confounders that I would think you would want to look at. And I know one of the criticisms from, I think one of the reviewers of the Southampton studies was that, that the studies looked at mixtures rather than single additives.

And personally, that didn't concern me. I mean, it concerns me given the lack of studies on single additives. But in reality these children are consuming mixtures. And I think it's important for us to be able to look at single additives but also

mixtures at the same time.

One question I did have and then I'll give up because I've hogged too much time, is are their tests for allergies to food colorings? I mean, because it seems like that if you doing this study, I would, if that's available, I would want to test all participants for allergies to those food colorings, if that test is available.

DR. THURMOND: That's a good question and I agree. But getting back to your dosing approach as I say, most, most are most colors are given as mixtures. And you're right, a lot of -- some drinks have two maybe more colors included in them.

The study I referred to from clinical trials that is still recruiting, they changed their approach early on from using color mixtures to using chocolate cookies just as you mentioned. So, you know, but they still haven't gotten the study off the ground, but that seems to be the way to go or at least, you know, if you can make sure the kids don't taste something odd in the chocolate cookies.

DR. ZAJAC: Also, I recall that some of the

studies did have a skin prick step as part of the conduct of that study looking for an immunologic response. And for Yellow 5 that is known to cause an allergic type reaction, which is one of the reasons we that it has to be declared in all foods, including butter and an ice cream. Which would normally be exempt from having to make that declaration because of that concern.

DR. KOWALCYK: Just to follow up, I mean, one thing that you could consider in the design of these studies is matching on potential confounding variables. Matching cases and controls, and that's one thing it didn't really seem like they were doing that in their studies.

The other thing that I would -- ideally you would have a study that would look at and collect data on the frequency and quantity of consumption.

And if you can't do that, I would minimally look at high versus low or no exposure. It seemed to me that a lot of the studies, and maybe I wasn't -- maybe I misinterpreted because I didn't go read every individual study that looked at exposure versus non

exposure, and you know, you can have someone that's exposed on a very low level sporadically or even daily versus someone that is exposed on a high level. I have a 15 year old son at home, so I know exactly what he eats and he's high exposure compared to compared to my daughters.

But I think that you can also look at different cutoff levels or different categories of exposure and we might find significant results when we start stratification, but that would require a larger sample sizes.

DR. THURMOND: Thank you.

CHAIRMAN MCLELLAN: Cynthia.

DR. AFSHARI: Yes. You know, I'll just come back again. I mean, these discussions around some of these trials and the confounding elements. I mean, when I hear about chocolate cookies, I think about sugar and caffeine and you know, factors like that and what they play into some of those end points.

But I just wanted to come back to my comment earlier and I think has been picked up around some of the classic toxicology and pharmacology. And if we

think about the toolbox we have to normally look at, you know, various receptor binding activities and things of these types of molecules. I mean, there is the ability and one of the things that FDA does really well, as well as NCTR and NTP, is this overall weight of evidence. And a lot of times it is the negative data.

You know, if you aren't seeing any kind of reactive binding in a tube, so to speak from a biochemical perspective to you know, neural receptors and things like that, that's one weight of evidence. The fact that you don't get penetration into CNS past the blood brain barrier. You know, again, it's another weight of evidence thinking about short term exposures are very low levels again is adding to weight of evidence.

And so, I think those types of data, as well as you know, I think has been picked up. I mean, there are immunotox-type of assays that can be run. I think also if we looked at, you know, compounds or other things that activate histamine or that people have allergic responses, those aren't associated with

ADHD. You know, there's just different pieces of evidence that I think could be brought to the table in a very systematic way that we would, as we're looking at other compounds be it environmental, chemical, pharmaceutical that we think about from a tox and a pharmacology perspective that we should bring as part of the total package here in the assessment given the complexity of the clinical picture and some of that data.

CHAIRMAN MCLELLAN: Okay. While we have sort of a lag in comments here, my own interpretation, I do not see this causal link. I agree that it may be, it's just that we haven't got the right data, but I'm certainly not seeing it right now, personally.

The link in terms of treatment with ADHA, I really think that comes back to the how do you measure this whole issue of who does that measurement and how do you get that to an objective status?. And again, I do not see that. I do believe that we have been talking about now some new approaches that are really quite exciting.

I fully agree. This conversation about

power analysis. I've been a passionate outspoken person about regard for power analysis and need for it. I would hope that that study -- that gathering, the workshop that was done at the University of Massachusetts that laid out specific and direct approaches to answer this specific question, will offer guidelines for future studies. I think that's very powerful. And I'm really curious about the Bayesian work and the opportunity to drive yourself clearly to a causal link analysis with that. So neat technique and I'd be curious how that works.

Ted.

DR. REISS: So since we're trying to summarize, I'll go down your path there, Mark.

I also agree that from what was presented and what we've read about it, that there isn't any new information that would really necessarily today change the point of view or the perspective on both number one and number two.

And I agree with my colleagues around sort of the potential approaches that you can go forward to put the package together of information that would

weigh into either the association or the causal relationship. Here we talked about the preclinical information that could be useful and so on.

The problem that we have here is that we're not trying to show an effect, but we're trying to prove a negative, which we've sort of talked about so that it seems, you know, other than sort of piecing together the other bits of information, the only potential path forward would be to have a sort of a collaborative -- a standardized clinical trial as Mark was talking about from a methodologic point of view that excludes an effect with a certain level of certainty. That would probably be the only way forward. The FDA has done that with cardiovascular risk, for example, and so on. So that might be a potential path forward.

CHAIRMAN MCLELLAN: Any further comments? Committee members on the phone, you're welcome to chime in.

DR. NOLAN: Mark --

CHAIRMAN MCLELLAN: Go ahead Lisa.

DR. NOLAN: One thing that strikes me as an

opportunity is there's some recent studies that find a genetic link to ADHD and a comparison group of those with the link and those not, that show signs of ADHD may be useful test group to look at some of these issues.

CHAIRMAN MCLELLAN: Thank you. I'm just going to let us sit here for just a second.

DR. ZAJAC: I just wanted to add something regarding blinding, it was the issue that was brought up earlier here. And blinding is extremely important in a placebo controlled challenge test. And that was one of the deficiencies we noted in the McCann study that was done. Is there wasn't a test to ensure that the parents were blind -- properly blind. Instead they used an independent group for that.

And in terms of how you establish the placebo to make it color equivalent to the challenge drink in that test, I believe they use beet root powder because the beverage was red. So for the placebo I believe it was they used beet root and then the challenge had the certified colors in it.

CHAIRMAN MCLELLAN: Thank you. Laura.

DR. TOSI: Really a question more than anything else.

In the readings that we got, there were some animal models and yet when we were here, we heard it doesn't matter really because it's not crossing the blood brain barrier. I'm just a little bit confused about whether there is some good animal data that we should be taking into consideration or not.

CHAIRMAN MCLELLAN: Is it possible, Scott?

DR. THURMOND: Good question. Which means I probably don't have an answer for you, but yeah, when the Food Advisory Committee made a recommendation, they talked about doing a developmental neurotox study and we went back and looked at the literature and there was no good animal study. The animal studies we found were not, could not be used to assess human hyperactivity or intolerance to any compounds.

You know, there may be some other models that we have not thought about animal models. I mean, obviously we're not going to do primates, but you know, as far as I know the animal models are not the best choice for those types of studies.

CHAIRMAN MCLELLAN: Kathryn.

DR. BOOR: So I have to say I'm struggling with trying to imagine the perfect set of studies because it's not going to be a study. It's going to be a set of studies to try to get to the point where you can look at causality. You need -- for causality to some extent, there needs to be some reductionism in thinking that we -- I haven't heard or seen or read in any of these studies that get us to that point. And so I guess I leave this set of comments with the question.

Which is, is it possible for a consortium to come up with what approaches the design of an ideal study and a way for that sort of consortium to work with the right team to start to do those kinds of studies? Because I think it's so easy for us and reading these papers to see what others did wrong, but how can we do it right? And I think that's what I find missing so far.

CHAIRMAN MCLELLAN: Thank you. Tony.

DR. BAHINSKI: One question and one kind of follow- up comment. And the question is more about my

naiveté about the development of the blood brain barrier. But I seem to remember that, you know, up to a certain age, you know, the permeability changes over time. Have people looked at that to see if these compounds, you know, when you're a very early age you have much more promiscuity of crossing the blood brain barrier versus later as an adult it works much tighter.

DR. THURMOND: To the best of my knowledge I am not aware of any studies that were done that, but you know, there may be some out there that we've missed.

DR. BAHINSKI: Okay. And the comment was around -- one of the previous Board members brought up around the association with the ADHD genes.

I wonder if there's a way to leverage, you know, these companies like 23andMe and others out there that have genetic databases. And I know often as part of the process if they, the patients or the people that are getting that genetic background, if there's a study or a clinical trial that may be of relevance to their conditions.

o for ADHD, that associated gene, you know, would they be willing to participate in a study? Because I know recruitment for some of these studies can be very difficult to get. So that might be a way to identify a population that might be willing to participate in some of these clinical trials. Just a thought.

CHAIRMAN MCLELLAN: Scott.

DR. STEELE: Just following up Kathryn and Ted's comments. I concurred with your summary for questions one and two, but related the study development and the challenge, I was just thinking of some of the issues around rare disease and novel trial designs they're doing there and small sample size issues and challenges with diagnosis. And whether it's -- there's been a lot of public-private partnerships in that space. So I think the consortium idea to design and launch some smaller targeted studies might be a useful approach.

CHAIRMAN MCLELLAN: Good suggestion. Dojin, please.

DR. RYU: So I agree that there is no

perfect or good animal model to study the link this color where they ADHD.

And so, I tried to look it up, but they can provide some pieces of information that can connect dots. So in other words, if animal model could provide some hints and would there be any way to say, suggest a set of models or ways to have better understanding or the better linkage between the behavioral changes and the mechanistic causes?

So that would be, you know, question/comment that I could not very much understand or to link all the pieces of the data from the animal study, cannot be directly linked to the ADHD.

So maybe a consortium or the concerted effort to bring that you know, different models to understand better how that may be linked to ADHD. And that with another part as some studies used polyunsaturated fatty acid in alleviating the symptoms.

So in that case, if any mechanisms like antioxidant or the oxidative stress being the potential factors affecting that, then that could be

also you know, included because the clinical studies are using that fatty acid being more in numbers in recent years, then any other clinical studies approved or ongoing.

So in that case, if you include that factor, there got to be something that we can better connect if you will.

DR. FERGUSON: Hi, this is Sherry Ferguson. I'm on the phone and I just wanted to make a comment about the animal models. I think a developmental neurotoxicity study would give us a lot of information regarding changes in attention, changes in activity levels in rodents.

But before we could even proceed with that, we'd have to know a lot more about the metabolism and excretion and how similar that is in rodents to humans. And I don't think we have that information in humans yet.

CHAIRMAN MCLELLAN: Thank you, Sherry.

Okay. I am going to draw our discussion period here to close this. This has been a very interesting challenge. I purposely took us through

this for the purpose of discussion and exchange of opinions because I think up front we all recognize there's a lot happening here and it's certainly a mishmash of data that you're trying to individually assess and put out there. And I appreciate those who came forward and engaged in that conversation.

I hope I think on all three of the questions you heard a sense of engagement and I hope you all, particularly in the third one, where you're looking for a new directions may have come up with some there that may up may be of help. And so, thank you all for being part of that.

We will be having lunch and the committee will be entering into a training session. We'll be engaging with Amy Abernethy and looking forward to that and talking about our future as a Board. Be aware that April and October, we'll have two meetings ahead coming up. So keep that in mind.

Rakesh will be getting in touch with us regarding those possible dates. So speaking of which, is there anything we need to add before I close out?

MR. RAGHUWANSHI: No.

CHAIRMAN MCLELLAN: Good. Then let's call this this formal meeting of the Board closed at this point or complete, and then we'll have lunch and move into our training session. Thank you all.

(Whereupon, at 12:29 p.m., the Science Board meeting was adjourned.)