

1 SCIENCE BOARD TO THE FOOD AND DRUG ADMINISTRATION

2 ADVISORY COMMITTEE MEETING

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9 Monday, October 7, 2019

10 8:30 a.m.

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18 U.S. Food and Drug Administration

19 Building 31

20 10903 New Hampshire Avenue

21 Silver Spring, Maryland 20993

22

## 1 PARTICIPANTS

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## 1 PROCEEDINGS

2 (8:38 a.m.)

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

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

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

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

2 Thanks.

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

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

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

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

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

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

1 defined as chemical food safety.

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. WILSON: Good morning Caroline Wilson,

1 Associate Director for Research in the Center for  
2 Biologics.

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

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

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

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

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

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

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

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

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

1           Based on the agenda for today's meeting, no  
2 conflict of interest waivers have been issued. We  
3 have one open public comment period scheduled for  
4 10:00 a.m. with two members of the public having  
5 requested to speak.

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

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

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

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

22           DR. NOLAN: Lisa Nolan, Dean of the College

1 of Veterinary Medicine at the University of Georgia.

2 CHAIRMAN MCLELLAN: Thank you Lisa. Minnie?

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

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

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

22 I do not necessarily expect this to come to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Our Office of Laboratory Safety is also

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

4 I'll end by congratulating our Health  
5 Informatics staff, which created and continues to  
6 develop Precision FDA. This is a virtual laboratory  
7 for analysis of data sets by scientists both inside  
8 and outside of the FDA. Precision FDA received the  
9 2019 Federal IT Innovation Award and we're proud of  
10 those who made that possible.

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

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

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

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

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

14 RADM HINTON: Absolutely.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 Action Plan, I think is what it stands for.

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

7 I'm thinking particularly of a report that I  
8 chaired couple of years ago looking at the ability of  
9 some of the food safety laboratories, your state  
10 partners, to be able to upload data into FDA directly  
11 and there were some challenges around that.

12 So I was wondering if you could just expand a little  
13 bit on how broad TMAP will be and will it be looking  
14 at ways to better facilitate sharing from your  
15 external partners?

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

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

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

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

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

5 CHAIRMAN MCLELLAN: Yes, Cynthia.

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

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

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

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

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

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

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

1 issues.

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

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

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

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

1 our engineering and analytic capabilities.

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

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

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

20           Dr. Marks, anything to add?

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

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

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

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

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

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

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

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

22 Two examples of what we're doing right now.

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

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

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

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

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

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

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

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

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

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

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

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

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

8 DR. WILSON: Yes, I am.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14           So the next major bucket that the committee  
15 report talks about is in research collaborations. The  
16 first recommendation there is to further expand  
17 collaborations and personnel exchanges with a variety  
18 of agencies addressing similar emerging areas. And we  
19 do that through collaborations in workshops. So in FY  
20 '18, we had a collaboration with NIH to have a  
21 workshop on the science and regulation of life,  
22 microbiome-based products used to prevent treat or

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

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

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

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

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

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

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

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

1 there. Sorry. Okay. So there we go.

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

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

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

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

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

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

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

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

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

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

4           Impact and sustainability of core  
5 facilities. The recommendation was to provide  
6 necessary resources with sustainable funding models,  
7 including how they could be shared more broadly within  
8 the FDA. So the Regulatory Science Council last year  
9 developed a new funding model for core facilities. We  
10 actually it developed in FY '18 and phased it in, in  
11 '18 and implemented it in '19.

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

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

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

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

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

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

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

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

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

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

1 whatever doses and just try it.

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

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

16 Peter, did you want to add anything to that?

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

1 this issue that they tend to study complex mixtures.

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

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

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

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

1 with other department -- other agencies of the  
2 government.

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

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

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

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

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

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

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

2 I think that answers your question.

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

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

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

1 DR. REISS: Good. Thank you.

2 CHAIRMAN MCLELLAN: Thank you. Cynthia.

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

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

1 research.

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

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

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

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

7 CHAIRMAN MCLELLAN: Scott.

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

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

15 DR. WILSON: Yes.

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

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

22 But in addition to the horizon scanning,

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

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

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

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

17 DR. WILSON: Great.

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

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

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

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

19           DR. STEELE: Thank you.

20           DR. WILSON: Okay. I'm going to push on.

21 Oh, is there one more question? Sorry.

22           CHAIRMAN MCLELLAN: We have one more. Go

1 ahead Sean.

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

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

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

22 Those are more cost efficient because if

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

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

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

1 for the scientists within the agency.

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

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

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

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

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

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

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

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

22           At the time of this review, there was quite

1 a lot of expertise and personnel gaps and OBE has  
2 really done a lot to reduce personnel vacancies over  
3 the past year. For example, medical officer or  
4 reviewer vacancies were reduced by 30 percent. And  
5 again, to address these expertise gaps, they're really  
6 looking at bringing in staff who have new skills such  
7 as understanding how to harness real world evidence,  
8 using developing tools to support science-based  
9 patient input, the Sentinel Initiative, innovative  
10 clinical trials, which again is a very big piece of  
11 21st Century Cures Act, as well as model informed drug  
12 development. Next slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17           Assuring strategic and budget planning, that  
18 appropriate distribution of resources are weighted  
19 toward emerging and rapidly evolving areas and that  
20 plan should enable flexibility. So I covered the  
21 general approaches but also more specifically, in FY  
22 '19 CBER was grateful to receive new funding authority

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

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

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

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

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

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

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

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

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

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

15 So OTAT, and its predecessor Offices of Cell  
16 Tissues and Gene Therapies, actually have had a long  
17 history of collaborative development of standards for  
18 vectors. Actually, I can proudly say I was the person  
19 who started this with the first replication competent  
20 retrovirus standard that was available through ATCC in  
21 the mid-nineties. That was followed by an adenovirus  
22 5 standard. And then, more recently there's been a

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

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

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

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

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

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

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

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

2 Next slide.

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

10           Prepare -- okay. We are coming to the end.

11 Next slide.

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

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

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

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

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

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

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

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

22 So I'll stop there and happy to answer any

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

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

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

11 Scott, go ahead.

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

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

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

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

11 All alright. Well thank you again.

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

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

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

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

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

11 (Recess.)

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

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

22 So we're now going to conduct our open

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

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

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

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

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

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

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

17                   MR. RAGHUWANSHI: They have.

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

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

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

12 EFSA re-evaluated synthetic food colors in  
13 the last 10 years is part of its broader food additive  
14 re-evaluation program. Six of the FD&C colors are  
15 approved for use in Europe. No concerns were raised  
16 about safety or exposure and in most cases the  
17 previous acceptable daily intakes were retained.

18 JECFA has also re-evaluated seven FD&C colors since  
19 2011. Acceptable daily intakes were developed by  
20 conducting risk assessments on each color based on a  
21 relevant endpoint of toxicity other than neural  
22 behavioral effects.

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

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

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

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

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

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

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

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

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

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

3           In fact, a diet excluding FD&C colors has  
4 the lowest impact in improving behavior relative to  
5 other interventions as noted and multiple meta-  
6 analyses. Those that have found a benefit were unable  
7 to do so conclusively. Nigg and others in 2012 noted  
8 methodological limitations. Stevenson and others in  
9 2014 concluded that the effect size was too small to  
10 be of value and the patient population for which an  
11 elimination diet would benefit remains uncertain.  
12 These authors came to similar conclusions as others  
13 before, that the data do not support dietary  
14 restriction including the elimination of food color  
15 additives as an efficacious treatment for ADHD.

16           One systematic review, Pelsser and others in  
17 2017, performed a critical analysis of two meta-  
18 analyses that evaluated the evidence associated with  
19 elimination diets of food colors and ADHD and  
20 concluded the results do not support restriction of  
21 food colors for the treatment of ADHD. That same  
22 study suggests that a few foods diet approach has the

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

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

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

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

1 evidence-based intervention for ADHD.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22           There was another study in 1997 that did say

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

9 Okay. I'm trying to advance. Okay.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 So in terms of any research going forward,

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

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

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

22           The Pelsser review acknowledged that the

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

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

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

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

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

22           Thank you.

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

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

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

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

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

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

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

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

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

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

7 So Dr. Keefe.

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

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

22 Today, we want to revisit this topic with

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

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

16           DR. THURMOND: Thank you, Dr. Keefe.

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

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

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

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

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

1 coffee is in that.

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

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

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

1 treatment of childhood hyperactivity.

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

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

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

1 allowed for use in this country in foods and sodium  
2 benzoate. Mix B was Sunset Yellow, carmoisine,  
3 Quinoline Yellow, not allowed for use in the US,  
4 Allura red or Red 40 and sodium benzoate.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 containing these FD&C colors.

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

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

1 color additives and their possible role in ADHD.

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

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

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

4           Okay. The Pelsser, study we've just found  
5 that. We did a literature search in early or mid-  
6 2019, which is why we may not have picked up the study  
7 that Mr. Cox noted in his presentation. But the  
8 Pelsser study was published in Plos One in 2017 and  
9 the article title was "Diet and ADHC: Reviewing the  
10 evidence, the systematic review of meta-analysis of  
11 double blind placebo controlled trials evaluating the  
12 efficacy of diet interventions on the behavior of  
13 children with ADHD."

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

1 should not be advised as a general ADHD treatment.

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

20           And thank you for your attention.

21           CHAIRMAN MCLELLAN: Thank you Scott.

22 Appreciate that. And I think that's the end of the

1 oral presentations here.

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

6           DR. CHELONIS: Yes, John is here.

7           CHAIRMAN MCLELLAN: Thank you John.

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

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

14           DR. FERGUSON: Well this is Sherry Ferguson  
15 and I am Division Director of Neurotoxicology at the  
16 National Center for Toxicological Research. I've been  
17 doing work in Developmental Neurotoxicology for almost  
18 30 years now. I'm not sure I would consider myself an  
19 expert on color additives and their effects, but that  
20 gives you just a bit of history.

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

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

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

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

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

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

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

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

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

22          CHAIRMAN MCLELLAN: Barb.

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

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

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

9 DR. THURMOND: Sorry.

10 DR. KOWALCYK: So the the second question I  
11 had was, I believe it was Dr. Cox had mentioned a  
12 more recent meta-analysis by Cagigal, et al. and from  
13 2019. I did a quick search online and could not find a  
14 copy of that meta-analysis. Have you looked at it?

15 DR. THURMOND: No.

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

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

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

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

6 CHAIRMAN MCLELLAN: Sure Minnie. This is  
7 Mark.

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

20 Sorry, that is my question.

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

1 DR. SARWAL: Was it not clear?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 CHAIRMAN MCLELLAN: Sean.

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

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

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

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

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

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

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

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

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

17           DR. THURMOND: Yes.

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

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

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

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

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

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

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

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

22 I think the second one was where Dr. Reiss

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

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

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

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

3 CHAIRMAN MCLELLAN: Thank you. Barb.

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

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

16 You know, there were, as I noted, there were  
17 10 criteria that our expert reviewer was looking at in  
18 terms of, you know, the studies that we had reviewed.  
19 And you know, it's difficult to find studies that have  
20 all the components you would like to have.

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

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

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

10 CHAIRMAN MCLELLAN: Very good. Barb.

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

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

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

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

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

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

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

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

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

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

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

19           CHAIRMAN MCLELLAN: Thank you. Dojin.

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

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

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

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

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

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

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

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

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

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

1 safer? Do we know that?

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

12 Now, within those categories, not all  
13 products contained the color additives, you would have  
14 variability from some products would contain a FD&C  
15 color additive, but maybe another product wouldn't.  
16 Like macaroni and cheese. Some brands contain Yellow  
17 5, Yellow 6, others had gone to annatto or turmeric in  
18 their formulations. And so, it just really is a kind  
19 of a formulation based whether they had the FD&C color  
20 additive.

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

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

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

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

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

22           Did I get all the questions?

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

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

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

1 FD&C colors.

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

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

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

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

22 The question that I have also, we've also

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

9           How was that done and how is it maintained,  
10 especially in these older studies that are from the  
11 '70s and '80s, where maybe people didn't pay attention  
12 to those? Do you have any thoughts or information  
13 about that?

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

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

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

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

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

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

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

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

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

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

1 testing of individual samples.

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

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

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

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

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

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

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

18           DR. BAHINSKI: Thanks Mark.

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

1 other studies that have been presented to the Science  
2 Board.

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

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

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

1 these kind of Registered Reports.

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

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

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

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

1 DR. THURMOND: Exactly.

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

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

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

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

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

6 CHAIRMAN MCLELLAN: Just a quick side  
7 comment regarding access to data. Of course, since  
8 2013 the OSTP guidance for extramural funding  
9 requiring public access is changing everything in the  
10 universities. Most universities are taking that  
11 approach that it is the data must be accessible,  
12 whether it's a negative result or not, it must be  
13 available. So that may change things in the future  
14 for us. Barb, you were next.

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

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

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

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

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

22           Now if your sample size is so large that you

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

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

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

22           So that was something that I wanted to point

1 out that that may be able to be used.

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

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

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

1 mixtures at the same time.

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

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

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

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

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

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

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

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

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

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

12           DR. THURMOND: Thank you.

13           CHAIRMAN MCLELLAN: Cynthia.

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

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

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

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

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

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

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

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

22 I fully agree. This conversation about

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

12 Ted.

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

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

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

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

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

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

20           DR. NOLAN: Mark --

21           CHAIRMAN MCLELLAN: Go ahead Lisa.

22           DR. NOLAN: One thing that strikes me as an

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

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

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

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

22 CHAIRMAN MCLELLAN: Thank you. Laura.

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

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

9 CHAIRMAN MCLELLAN: Is it possible, Scott?

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

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

1           CHAIRMAN MCLELLAN: Kathryn.

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

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

20           CHAIRMAN MCLELLAN: Thank you. Tony.

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

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

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

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

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

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

8           CHAIRMAN MCLELLAN: Scott.

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

20           CHAIRMAN MCLELLAN: Good suggestion. Dojin,  
21 please.

22           DR. RYU: So I agree that there is no

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

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

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

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

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

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

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

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

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

19           CHAIRMAN MCLELLAN: Thank you, Sherry.

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

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

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

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

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

22 MR. RAGHUWANSHI: No.

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

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

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